Report of the

National Commission on Diabetes

to the Congress of the United States

Volume III

REPORTS OF COMMITTEES, SUBCOMMITTEES, AND WORKGROUPS

Part 1

SCOPE AND IMPACT OF DIABETES (I)

"The National Diabetes Mellitus Research and Education Act" (Public Law 93-354), signed by the President on July 23, 1974, directed the appointment of a National Commission on Diabetes whose charge was to formulate a long-range plan of research and education to combat diabetes mellitus. The Commission submitted its report to Congress on December 10, 1975.

REPORT OF THE NATIONAL COMMISSION ON DIABETES

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Volume III

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Part 1

SCOPE AND IMPACT OF DIABETES (I)

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VOLUME III

REPORT OF THE COMMITTEES,
SUBCOMMITTEES, AND WORKGROUPS

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VOLUME III

REPORTS OF COMMITTEES, SUBCOMMITTEES, AND WORKGROUPS

FOREWORD

As a means of fulfilling its legislative mandate, the National Commission on Diabetes formed various committees, subcommittees, and workgroups to address the problems of diabetes. This volume contains detailed summaries of their investigations.

Four major committees were established: Scope and Impact, Treatment, Etiology and Pathology, and Education. Each operated in the way most appropriate for it to carry out its charge--usually through subcommittees and workgroups assigned to focus on key topics within the given committee's area of responsibility. Parts 1-5 of this volume contain the workgroup reports of these four committees.

In addition, the Commission formed other workgroups to address other specific topics relevant to diabetes. These were concerned with Diabetes Research Training Centers, the Veterans Administration, the Center for Disease Control, Data Resources in Diabetes, and Federal Resources. Part 6 of this volume summarizes the reports of these additional workgroups.

The workgroups and their consulting staffs included experts in diabetes and other medical/scientific fields--and lay persons with special expertise--from all over the U.S. The result is an extensive collection of reports, each centered on a defined area of the broad subject, which attempts to review comprehensively the state of knowledge and research in diabetes in this country, and--on the basis of this review--makes recommendations for future efforts against the disease. These workgroup reports, along with other supportive materials presented elsewhere in this Report, provided important background for the shaping of the National Commission's Long-Range Plan to Combat Diabetes described earlier in Volume I.

Although the order of presentation may vary in some reports, each workgroup was asked to organize its report to include the following matters in relation to its specific topic:

- Statement of the problem and its impact

- State of the art

- Future directions (goals, objectives, and approaches)

- Backup references and/or bibliography

- Recommendations (project summaries)

At numerous points, the workgroup reports overlap and cross-reference each other. This is to be expected, and indeed is necessary and desirable in the large configuration of all the reports. We have called explicit attention to some cross-referencing possibilities in the text of the reports, and the reader will note other such possibilities as he looks over this volume's table of contents or as he reads the reports. Different workgroups sometimes dealt with the same (or a similar) topic; for instance, both the Committee on Scope and Impact and the Committee on Etiology and Pathology have workgroup reports on the genetics of diabetes--with each group bringing its own approach and emphasis to the topic. Occasionally, groups worked collaboratively, but--given the limited time for investigation, assimilation of data, and the preparation of these summary reports--there was generally no attempt to collate studies on the same topics across workgroups. Nor was such collation thought especially desirable for our purposes.

In some instances, there may be apparent discrepancies between conclusions drawn by one workgroup and those drawn by another dealing with the same or similar material. These inconsistencies may be due to the use of data from different sources, or they could involve different extrapolations from the same data. Also, the fact of incomplete or insufficient information may have invited differing conclusions on the same topic.

To the extent that time has permitted, these reports have been revised and edited, but are still considered by their authors as working drafts which are not as polished or complete as they would have liked. Not only did the workgroups operate under severe time constraints in preparing the reports; they were also frustrated at times by the lack of adequate contemporary data--crucial information simply not yet available in diabetes studies. The reports, then, should be regarded essentially as working papers intended to be descriptive and suggestive rather than definitive.

It should be noted that, while the project summaries and recommendations for each workgroup represent the consensus of that group at the time its report was prepared, it was understood that these recommendations were to be further prioritized and modified by the National Commission as it prepared its final recommendations. Other matters in the reports may now be similarly "historical"; for instance, references to the possibility of a National Diabetes Council should be updated to become references to a possible National Diabetes Advisory Board.

The reports point to original sources as much as possible, and the reader is encouraged to follow up by referring to these primary materials for the full context. Relevant bibliography and/or references accompany each individual report, usually coming at the end of the main body of the text. In some reports, short lists of references may appear within the text itself following specific sections. Even at the cost of some repetition (since various reports will often cite the same references), we have thought it best to maintain the integrity of each workgroup report by keeping its references--and its tables and figures--with it, rather than placing these all together at the end of this volume. The documentation form of Index Medicus has been used for referencing, with the exception that (in the interest of providing maximum information) we have included, where possible, the full list of names when there are multiple authors of a publication. Documentation in this volume is as complete and accurate as time limitations upon the editing permitted.

REPORT OF THE COMMITTEES,
SUBCOMMITTEES,
AND WORKGROUPS

1

Report of the

COMMITTEE ON

SCOPE AND IMPACT OF DIABETES

to the

National Commission on Diabetes

Chairman:

Buris R. Boshell, M.D.

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COMMITTTEE ON THE

SCOPE AND IMPACT OF DIABETES

of the

NATIONAL COMMISSION ON DIABETES

Roster of Participants

Chairman:
Buris R. Boshell, M.D.

Workgroup Chairmen:

Peter H. Bennett, M.D.
Epidemiology

George K. Tokuhata, M.D.
Mortality

Thaddeus E. Prout, M.D.
Morbidity

David L. Rimoin, M.D.
Genetics

John B. O'Sullivan, M.D.
Pregnancy

Paul S. Entmacher, M.D.
Economic Impact

Dorothea W. Puckett, R.N., Ph.D.
Socioeconomic and Psychosocial
  Impact

William Wishner, M.D.
Social Impact

Participants

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Robert Anderson, M.D.
Robert Armstrong, M.S.
Mary Ashley
Lester Baker, M.D.
Edwin L. Bierman, M.D.
Elsie Carrington, M.D.
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Edward Digon, M.P.H.
Nancy Dixon, M.A.
Lee Ducat
Max Ellenberg, M.D.
Arnold Engel
Stefan Fajans, M.D.

O.P. Ganda, M.D.
Clifford Gastineau, M.D., Ph.D.
Saul Genuth, M.D.
Tavia Gordon
Kurt Gorwitz, D.P.H., Sc.D.
Jean-Pierre Habicht, M.D., Ph.D.
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Paula Kanarek, Dr.S.
William Kannel, M.D., M.P.H.
Gerald Kent, M.D.
Johannes Kobberling, M.D.
Joyce Kortman

Robert Knopp, M.D.
Stanley Kranczer, M.B.A.
Harvey Knowles, M.D.
Leo Krall, M.D.
Paul Madden
Alexander Marble, M.D.
Curtis L. Meinert, M.D.
Boyd E. Metzger, M.D.
Leona Miller, M.D.
Stanley Mirsky, M.D.
Bernice Morton, R.N.
James Neel, M.D.
Henry E. Oppenheimer, M.D.
Bobby Jean Purdue, M.S.N.
Hilda Richards, Ph.D.
Arlan L. Rosenbloom, M.D.
Martha W. Smith, M.S.
Jonas Sode, M.D.
Joseph Solowiejczyk
Robert Schwartz, M.D.
Karl E. Sussman, M.D.
H. St. George Tucker, M.D.
Manuel Tzagournis, M.D.
Kelly M. West, M.D.
Jack L. Werner, M.D.
Fred Whitehouse, M.D.
Louinia Mae Whittlesey
Donald Yett, Ph.D.
Donna Younger, M.D.
Jonathan Zonana, M.D.
William J. Zukel, M.D., D.P.H.

I. SUMMARY OF THE WORK OF THE COMMITTEE ON
SCOPE AND IMPACT

The latest data available to the Committee on Scope and Impact indicate that, in 1973, there were 4,200,000 reported diabetic patients in the United States--a more than 50% increase over the 2,700,000 reported in 1965. In addition, many diabetics are unreported, and conservative estimates suggest that, in 1973, there were over 10,000,000 people with diabetes in our country (about 5% of the population). Over 600,000 persons are newly diagnosed as each year. Mortality from diabetes is increasing as well, with approximately 100,000 deaths in 1973 attributed to diabetes as either the underlying cause or the contributing cause. These mortality data, which also have been shown to be under-reported, rank diabetes as the fifth leading cause of death in the United States. Severe complications of the disease include blindness, kidney disease, and cardiovascular disease, with diabetics suffering increased prevalence over the general population of blindness (25 times), renal disease (17 times), gangrene (20 times), and heart attack or stroke (two times). The economic impact of the morbidity and mortality of diabetes and its complications in 1975 is estimated to be about $6 billion per year.

The Scope Committee, and its workgroups, have agreed on a series of recommendations in three major categories:

- First, an improved understanding of the disease is essential to its ultimate cure and prevention. Epidemiological studies go hand-in-hand with research into the etiology and pathogenesis of the disease in securing this understanding.

- Second, long-term, prospective, collaborative epidemiologic studies are required to provide positive and negative clues for basic and clinical scientists to make their research more effective and to identify and measure those factors that have potential in the prevention of diabetes and its complications.

- Third, improved health and vital statistics data gathering and reporting are essential to accurately document the magnitude and impact of the disease and its complications so that the national priority for diabetes research and control programs can be established and justified and so that progress toward control and ultimate prevention may be measured.

To ensure that the ultimate findings of the Commission would receive wide support from the diabetes community and the Legislative and Executive Branches of the Federal Government, each workgroup was asked:

- to seek the broadest possible input from all elements of the diabetes community and the public at large, and

- to the extent possbile, to base any recommendations upon referenced facts and widely accepted data.

Exhibit 1 lists the workgroups of the Committee on Scope and Impact and their members (as of July 1975). These workgroups met and held discussions often during June, July, and August of 1975. The efforts of the workgroups were extraordinary in light of the time constraints placed upon their deliberations and the many changes and sacrifices in personal schedules required for participation in the workgroups. The Committee expresses its sincere appreciation for the cooperation and contributions of all the members and consultants. Exhibit 2 shows the portions of the Diabetes Mellitus Research and Education Act of special concern to the Committee on Scope and Impact.

EXHIBIT 1

NATIONAL COMMISSION ON DIABETE"
SCOPE COMMITTEE

9/75

OUTLINE OF WORK GROUPS

Work
Group

Committee of whole
Dr. Boshell
Mrs. Ducat
Mrs. Whittlesey
Mrs. Puckett
Dr. Haddock
Dr. Bennett
Dr. West
Dr. Entmacher
Mr. Oakes
Dr. Prout
Dr. Rimoln
Dr. O'Sullivan
Dr. Tokuhata
Dr. Habicht
Dr. Wishner
Dr. Andres

1. Definition — (Juvenile Onset) Insulin Dependent / (Adult Onset) Insulin Independent

2. Diagnosis
   - (Juvenile Onset) Insulin Dependent
   - (Adult Onset) Insulin Independent
   - Acceptable Control (in terms of diagnosis criteria)
   - Acceptable Criteria
   - Standardize glucose tolerance method
   - Standardize blood glucose level

Dr. Bennett
Dr. Habicht
Dr. Andres
Dr. O'Sullivan
Dr. Fajans
Dr. Bierman
Dr. Engel
Dr. Gorwitz
Dr. West

3. Epidemiology (Magnitude)
   - Prevalence
   - Incidence
   - Case-finding
   - Etiologic Factors
     - Diet
     - Obesity
     - Other

Dr. O'Sullivan
Dr. Carrington
Dr. Hoet
Dr. Knopp
Dr. Younger
Dr. Aiello
Dr. Schwartz

4. Pregnancy

Dr. Rimoln
Dr. Kobberling
Dr. Neel
Dr. Fajans
Dr. Zonana

5. Genetics
   - Summary of Theories
   - Pros & Cons
   - Alternatives

Dr. Prout
Dr. Prout
Dr. Bennett
Dr. Whitehouse

Dr. West
Mr. Gordon
Dr. Kannel
Dr. Tzagournis

Dr. Ellenberg
Dr. Zukel

Dr. Marble
Dr. Ganda

6. Morbidity
   - Microangiopathy — Eye / Kidney
   - Macroangiopathy — Heart / Brain / Legs
   - Neuropathy
   - Other — Ketoacidosis / Lactic Acidosis / Hyperosmolar Coma, etc.

Dr. Tokuhata
Dr. Kanarek
Dr. Moriyama
Dr. Armstrong
Dr. Entmacher
Mr. Digon

7. Mortality
   - Impact
   - Death Register or Certificates

Dr. Entmacher

8. Economic Impact

Dr. Wishner
Ms. Puckett
Mrs. Hoover

9. Social Impact

Dr. Tokuhata
Dr. Yett
Mr. Kranczer
Mr. Werner

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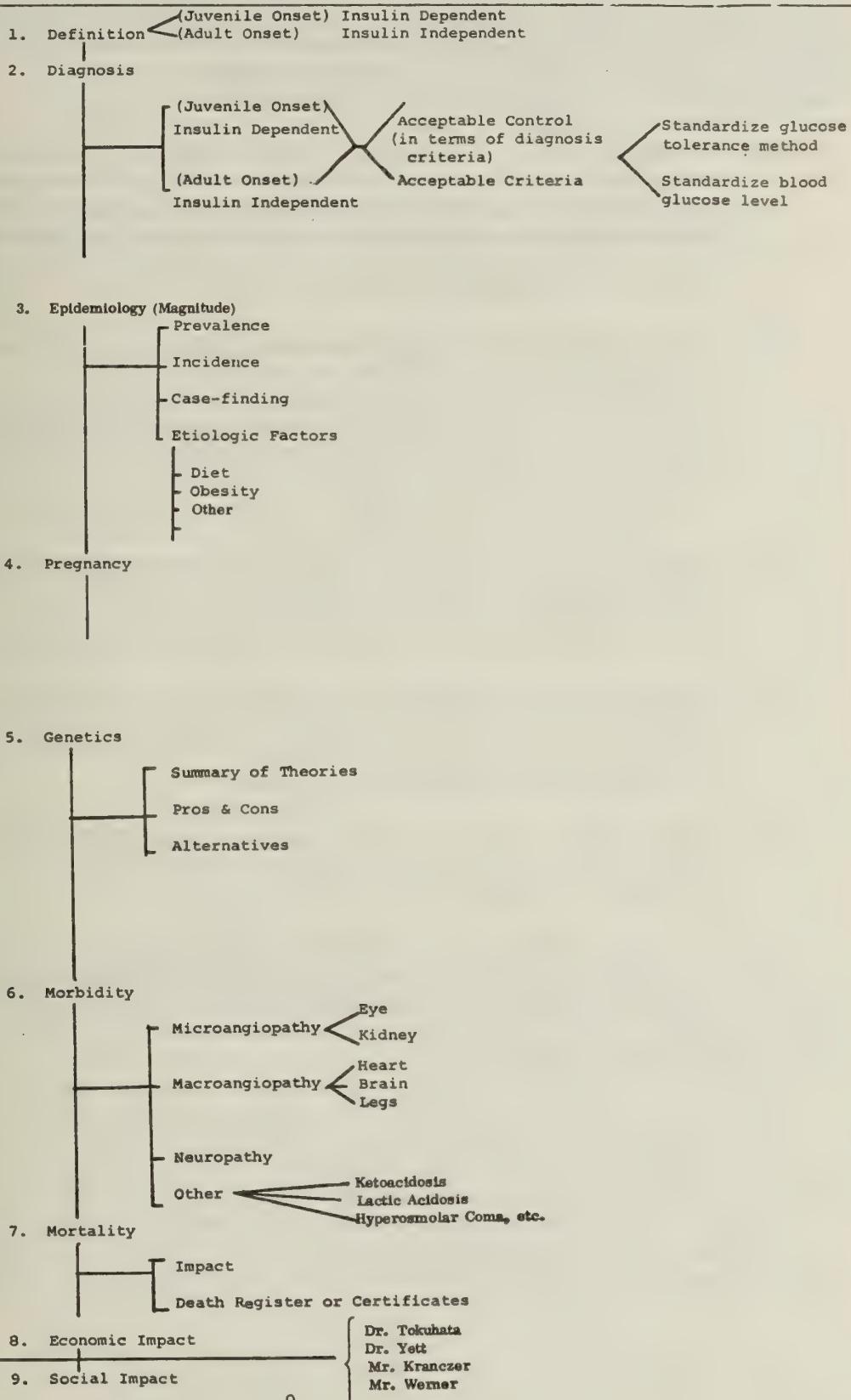
EXHIBIT 2

Excerpts from Public Law 93-354

Sec. 3. (e) <u>The Commission shall formulate a long-range plan</u> to combat dia-
betes mellitus.............. <u>Such a plan shall be based on a comprehensive
survey investigating the magnitude of diabetes mellitus, its epidemilology,
and its economic and social consequences.</u>.............. <u>The plan shall
include a plan for a coordinated research program.</u>.............. The
<u>coordinated research program shall provide for</u> --

    (1)   investigation in the <u>epidemiology, etiology</u>, prevention,
        and control of diabetes mellitus, including investigation
        <u>into the social, environmental, behavioral, nutritional,
        biological, and genetic determinants and influences</u>
        involved in the <u>epidemiology, etiology</u>, prevention, and
        control of diabetes mellitus:

    (2)   <u>studies and research into the basic biological processes
        and mechanisms</u> involved in the underlying normal and
        abnormal phenomena associated with diabetes mellitus,
        including abnormalities of the skin, <u>cardiovascular
        system, kidneys, eyes, and nervous system,</u> and evaluation
        of influences of other endocrine hormones on the etiology,
        treatment, and complications of diabetes mellitus;........

    (5)   <u>establishment of programs for the conduct and direction of
        field studies</u>, large-sclae testing and evaluation, and
        demonstration or preventive diagnostic, therapeutic,
        rehabilitative, and control approaches to diabetes mellitus;

    (6)   <u>the education and training of scientists</u>, clinicians,
        educators, and allied health personnel in the fields and
        specialties requisite to the conduct of programs res-
        pecting diabetes mellitus;

    (7)   <u>a system for the collection, analysis, and dissemination</u>
        of all data useful in the prevention, diagnosis, and
        treatment of diabetes mellitus;

    (f) <u>In the development of the long-range plan under subsection
(e)</u>, attention shall be given to means to assure continued development of
knowledge, and dissemination of such knowledge to the public, which would
form the basis of future advances in the understanding, treatment, and
control of diabetes mellitus.

A. <u>INTRODUCTION AND CHARGE TO THE COMMITTEE ON SCOPE AND IMPACT</u>

At the first meeting in early March 1975, the Commission decided that a national plan to combat diabetes mellitus should be based on the gathering and analyses of thorough data by several committees, each chaired by a Commission member. Three committees were established--Scope and Impact, Etiology and Pathology, and Education and Treatment (the last two subsequently would become separate committees). Each committee was asked to prepare a report covering three aspects of its area of emphasis: (1) the state of the art, (2) research needs, and (3) resources presently available and new resources (manpower and funding) required to meet these areas.

The charge of the Scope Committee was subsequently refined by definition of the topics to be included within the purview of the committee. Several important sources contributed to this definition:

- Pertinent portions of Public Law 93-354 (Exhibit 2)

- Suggestions of committee consultants

- The agenda of the Scope Committee Report (scientific session) held in conjunction with the Commission meeting on April 30, 1975, in Philadelphia

- Coordination with the other committees (particularly Etiology and Pathology) to ensure that no important area was overlooked

- The public testimony and discussions at Commission meetings

As a result of these efforts, the Scope Committee outlined its responsibilities to specifically address:

1. Definition and Diagnosis of Diabetes
2. Epidemiology
3. Mortality
4. Morbidity
5. Genetics
6. Pregnancy
7. Socioeconomic Impact
8. Economic Impact
9. National Diabetes Registry

For each of these topics, a workgroup (and subgroups) was established, and a chairman was selected to prepare written reports to the Committee (Exhibit 1). Each workgroup was asked to select its members and hold meetings so as to ensure the widest possible participation and contributions from experts and other interested contributors. (Subsequently, the charter of the National Diabetes Registry Workgroup was enlarged to encompass the broader issues of national data collection and reporting systems related to diabetes, and it operated thereafter as a workgroup separate from, although closely coordinated with, the Scope Committee.)

B. OVERVIEW OF WORKGROUP REPORTS AND PRIORITY RECOMMENDATIONS

1. INTRODUCTION

As its name suggests, the concerns of the Committee on Scope and Impact were inclusive. Because its workgroup reports are numerous, and often complex as well, we feel it will be helpful at the outset to present the following overall summary of workgroup findings as background to the ensuing full reports. These summaries also include some of the Committee's major recommendations to the National Commission.

At the end of this prefatory summary, we have provided a composite list of the Committee's project recommendations, which in turn is followed by a spotlighting of the priority recommendations of each workgroup.

2. BACKGROUND

The term "diabetes," coined from the Greek by Arataeus, means "capacity of a syphon," a good description of two symptoms of diabetes-- polyuria (excessive amount of urine) and polydipsia (excessive thirst). Diabetes has been known since about two thousand years before the time of Christ; a description of it exists in the old Egyptian Ebers papyrus scrolls. However, knowledge about diabetes did not advance until 1889, when Von Mering and Minkowski removed the pancreas from the dog and demonstrated the signs and symptoms of diabetes mellitus. It remained, however, for the Nobel prize-winning efforts of Banting and Macleod (and Banting's colleague Best) in 1921 to prove that an extract of the islets of Langerhans in the pancreas could alleviate the signs and symptoms of dia- betes in the depancreatized dog. This discovery, as applied to humans, has been the major and only breakthrough in the treatment of diabetes to the present. The fact that this breakthrough occurred over fifty years ago, in addition to the fact that the disease is becoming more widespread-- now affecting somewhere between 2% and 10% of the population--should suffice to stimulate a significant new look into the overall problem of diabetes.

3. DEFINITION AND DIAGNOSIS

One of the first tasks of the Scope Committee was to define diabetes mellitus. Since its diagnosis relies upon the definition, we strove for a rather universal definition, neither too specific nor too broad for that purpose. Therefore, we will consider diabetes to be a metabolic disorder characterized by hyperglycemia, a relative or absolute insulin deficiency, and (frequently) accelerated vascular disease. As a more precise classification of diabetes (and to minimize confusion), the Scope Committee recommends the use of the terms "insulin-dependent" and "insulin-independent," instead of the classic "ketoacidosis-prone" and "ketoacidosis-resistant" or of the commonly used "juvenile-onset type" and "adult-onset type" terminology.

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After the studies of Macleod, Banting, and Best, diabetes was thought to be an absolute insulin deficiency. Later, Galo, Thurston, and others demonstrated that a large amount of circulating insulin can be found in insulin-independent diabetics, and even that insulin can be extracted from the pancreas of the patient. It is highly possible that diabetes is a syndrome rather than a specific condition, and that future research needs a program that develops subclassifications of diabetes so that its etiology may be defined more specifically.

In the absence of the so-called elusive genetic marker or markers, we must be somewhat indirect and arbitrary in our definition of diabetes and its diagnosis. The diagnosis, as implied in the definition, is based on the glucose levels of the plasma. Other methods by which the diagnosis is sometimes established will be discussed below, in the report of the Definition and Diagnosis workgroup, but the oral glucose tolerance test (OGTT) remains the method against which other diagnostic criteria are measured.

A standard method for interpreting oral glucose tolerance tests is needed that can be applied to all ethnic groups and used as a test for methods. With a standard method, it will be possible to derive a basis for population screening and to derive principles on which to base glucose control. Because of these important and urgent needs, the compendium of present information on the scope of diabetes begins with a protocol for use in the interpretation of the OGTT.

Essentially, the Scope Committee is recommending that one follow the basic principles outlined by the Committee on Diagnosis of the American Diabetes Association, giving consideration to the important factors that affect the oral glucose tolerance test, such as liver disease; the intactness of the pyloris; the normality of the intestinal mucose; the previous nutritional state of the patient; the time of day the OGTT was performed; the age of the patient; the chemical, physical, and emotional stress; and the deleterious effect of certain drugs, especially the thiazide diuretics, oral contraceptives, and several hormones.

We also recommend that the glucose load be standardized with one gram per pound of body weight up to the level of 75 pounds, and thereafter to use approximately 40 grams per square meter of body surface—which would mean giving roughly 75 grams of glucose to the standard 70-kilogram man. This is somewhat less than that recommended by Conn and Fajans, and also slightly less than the 100 grams of glucose which frequently has been standard in the past. The glucose should be administered over a period of five minutes in 300 cc. of chilled water, and blood should be sampled for two or three hours. As outlined in Figure 1 in the Definition and Diagnosis workgroup report, the age factor is taken into consideration and standards are recommended. It may well be that these, which are based on the studies of Andres, will later require some degree of modification because of the fact that Andres' patients were all male, were all hospitalized, and received a loading dose of 1.75 grams of glucose per kilogram of ideal body weight. The Scope Committee also makes recommendations for interpreting test results.

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The diagnostic criteria form the basis for future epidemiologic studies and for a realistic comparison of studies done anywhere in the world. Unfortunately, the currently available epidemiologic data suffer from the fact that the criteria for definition and diagnosis and the methods for interpretation have varied from study to study.

4. EPIDEMIOLOGY

Over four million Americans were known to have diabetes mellitus in 1973. In addition, about six million persons are estimated to have undiagnosed diabetes. Approximately 600,000 persons are newly diagnosed each year. Both the prevalence and incidence of diagnosed diabetes have increased by more than 50% since 1965. Diabetes is associated with obesity, increasing age, poor economic status, and heredity—yet, the precise importance of these factors is unknown. The National Health Examination Survey and the National Health Interview Survey have provided useful information. However, they have markedly underestimated the true incidence of diabetes, and because of the lack of appropriate questions, have not provided the needed basis for estimating the mortality and the economic impact of diabetes mellitus. Again, these lacks will be approached as a part of a long-term study proposed at the end of this section.

5. MORTALITY

Diabetes mellitus has steadily increased as a cause of death since the turn of the century. It now ranks as the fifth leading underlying cause of death by disease in the United States, and estimates from some of the studies by our committee suggest that if it occupied the proper place, it would be third instead of fifth.

Many persons with diabetes die from its complications, mostly vascular pathology, yet the cause of death is not usually attributed to diabetes under the existing mortality reporting system. In addition, approximately 10% of the time, diabetes is not even recorded on death certificates according to the current rules of certifying cause of death. The poor visibility, which is primarily the result of existing methods of disease classification and selection of underlying cause of death, has led to an undue underestimation of the complex and significant health problem diabetes poses. Consequently, medical research and social action programs related to diabetes have not been supported at a level commensurate with its true importance as a major health problem.

A study conducted under the auspices of Dr. George Tokuhata in Pennsylvania demonstrated that if only the underlying cause is considered, as is conventionally practiced, the diabetes death rate for 1969 was 22 per 100,000 population in Pennsylvania. If the contributory and under-lying causes were considered together, the rate would rise to 150 per 100,000. If the number of unrecorded diabetics was added to that of all recorded diabetics, the overall diabetes death rate would reach as high as 161 per 100,000. If these statistics were applied to the total U.S.

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population, nearly 304,000 people, rather than the 38,000 officially reported, would be expected to die annually with diabetes in the United States. In other words, diabetes could well be considered the third leading cause of death.

Since diabetes is a common chronic disease affecting people of all ages, including infants and young children--with the juvenile-onset (insulin-dependent) type being especially serious in its medical complications--the potential benefit of an effective diabetes control program would be much greater than that of any other chronic disease program in which only adult populations may be affected. For such a program, it is quite important to devise a mortality reporting system which includes the age of onset of diabetes, as well as accurate geographic information. In the past, there has been some question about urban versus rural incidence of diabetes from the failure to report with exact precision the location of the individual with diabetes.

Our major goals in dealing with the problems of diabetes are to improve visibility of this disease as a leading cause of death and to develop better understanding of the nature and extent of diabetic complications as reflected in morbidity and mortality statistics. To achieve these goals, several different approaches may be used, some requiring immediate action and some requiring study and research for future projects.

6. MORBIDITY

Morbidity, which our committee categorized into microangiopathy, macroangiopathy, neuropathy, and ketoacidosis and coma, will have considerable overlap with the Etiology and Pathology Report. It has been our mission to describe the scope in these areas and to delineate coordinated investigative projects without being as specific in the latter as we might have been had we had full responsibility for these areas; nevertheless, a part of the long-term study proposed at the end of this workgroup report might help answer many of the blurry questions in the area of morbidity.

We have subdivided angiopathy into microangiopathy, with the primary concern for the eye and the kidney, and macroangiopathy, with involvement of the heart, the cerebral vessels, and peripheral vessels. We have then given specific sections to neuropathy and ketoacidosis and coma.

a. Microangiopathy

Besides microangiopathy involving the eye, diabetes is associated with excessive cataract formation and glaucoma. Cataracts occur four to six times more often in known diabetics than in nondiabetic patients. The National Eye Institute (NEI) estimates that there are almost 200,000 patients between the ages of 14 and 44 with cataracts in the United States alone; most of these cataracts are diabetes-related. Approximately 5%

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of patients attending diabetes clinics have primary glaucoma, compared to fewer than 2% in nondiabetics.

Glaucoma is one of the leading causes of blindness. Studies of the National Eye Institute indicate that approximately 62% of the juvenile diabetic population followed for ten years or longer will develop some retinopathy. Probably about 18% will develop proliferative retinopathy with the duration of diabetes extending over a period of 30 years. With nonproliferative retinopathy, the vision of 7.5% of patients with good vision becomes impaired annually, with approximately half of these ultimately going blind. The mortality rate in patients with advanced retinopathy is rapidly accelerated, and the mean annual mortality rate with advanced retinopathy approaches 15% per year. Thus, we are dealing with a major cause of blindness--of double import because it affects a young age group.

Renal failure is a common cause of death among diabetics. It is most often due to a specific diabetic glomerular pathology, but the effects of active infection and vascular changes as manifestations of the degenerative complications of diabetes are also contributive. In one survey, between 30% and 40% of diabetic patients admitted to indigent wards had urinary tract infections. Among outpatients, approximately 12% had white cells in the urine; and almost 40% had bacteriuria, in contrast to the presence of asymptomatic bacteriuria in less than 8% of the general population. Acute pyelonephritis is found more than four and one-half times as often in diabetics as in nondiabetics at autopsy, and acute cystitis approximately six times more often. High blood pressure is also related to the renal-vascular disease. Twenty percent of juvenile diabetics develop high blood pressure over the course of ten years, thereby acquiring another major risk factor for a vascular catastrophy.

Neuropathy is responsible for over two-thirds of the deaths of patients with proliferative retinopathy who die between 20-39 years of age. This is particularly disturbing with reference to those patients having the onset of diabetes before age 15. This figure is to be expected, however, in view of the increased prevalence of both nephropathy and retinopathy with the duration of diabetes. The average age from onset of diabetes to onset of azotemia is 17.3 years. About one-half of all juvenile diabetics now living will die of renal disease, with an average life expectancy of approximately 25 years after the diabetes is diagnosed. It should be emphasized that the fundamental problem of diabetic nephropathy will not be answered by renal transplantation or dialysis. It must be met by further studies of basic pathology.

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b. Macroangiopathy

Since, in persons with known diabetes, large vessel
disease accounts for about 75% of all deaths, it is quite
clear macrovascular disease is a massive problem warranting
high national priority. More data are needed in order
to develop strategies of attack that will have the greatest
effectiveness in relation to cost. We know, for example,
that amputation is required with distressing frequency,
but we do not know what percentage of diabetic patients require
amputation, and our knowledge concerning the epidemiology
of gangrene is quite primitive. More information is needed
on the prevalence, incidence, cost, and disability attrib-
utable to the various types of diabetic large vessel
disease. Also, more knowledge is urgently needed about the
factors which enhance or protect the diabetic from these
lesions. This again can likely be accomplished as a part
of the major study to be subsequently outlined here.

c. Neuropathy

The remarkable frequence of neuropathy is essentially
unrecognized, and reported prevalence varies widely as a
result of different diagnostic criteria. A conservative
estimate would be that about 25% of the patients with
diabetes are affected. Neuropathy plays a major role in
the development of the pathogenesis of other diabetic
complications, such as gangrene of the extremities, pyelo-
nephritis, and so forth. The relationship of diabetic
neuropathy to other aspects of the diabetic syndrome is not
well understood. There is a definite possibility that the
autonomic neuropathy may play a role in the fundamental
secretory aspects of hormones, and this is another area of
definite need from the investigative standpoint.

d. Ketoacidosis and Coma

The current magnitude of the problem of ketoacidosis/
coma in patients with diabetes mellitus in the United
States has been studied, and the following conclusions
appear warranted. Diabetic ketoacidosis or coma continues
to be responsible for 14% of all hospital admissions due
to diabetes. The incidence of ketoacidosis/coma through-
out the country did not change over the five-year period
of 1968-73. In the western sections of the country, the
incidence seems to have increased from 1970-73. Diabetic
ketoacidosis/coma currently accounts for 65% of all admis-
sions due to diabetes in the 0-19 year old age group and
40% of all admissions in the 20-34 year age group. The
incidence in none of the age groups declined in the five-
year period. The greatest increase over this period was

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seen in the 0-19 year age group in the Western section.
Ketoacidosis or coma is currently responsible for about
10% of all deaths in diabetic populations in Western U.S.
hospitals. Approximately 5-13% of ketoacidosis episodes
will end fatally. The fatality rates in patients with
hyperosmolar coma and lactic acidosis are not well
reported, but are probably much greater than in keto-
acidosis. Current health education and delivery of care
appear to be inadequate insofar as the prevention and
treatment of acidosis are concerned. This information
will undoubtedly be shocking to some who have developed
the feeling that diabetic coma had disappeared as a major
problem in the diabetic population.

7. Genetics

The Scope Committee has surveyed the incidence of diabetes, both the
projected incidence and the measured incidence. The projected incidence
involves genetic studies, and unfortunately, disagreement is widespread
about the genetic mode of transmission. While the familial tendency of
diabetes mellitus has been established and it is well recognized that
genetic factors are important in its etiology, there is still little
agreement about the nature of these genetic factors and how diabetes is
inherited.

8. Pregnancy

Pregnancy is the one area where casefinding probably is in order.
The studies of several individuals have indicated that detection of
abnormal carbohydrate metabolism and the institution of appropriate
therapy can have a very significant effect on the outcome of the pregnancy.
Therefore, it would appear that a detection program in those who are
thought to be at high risk is in order. This would include those with a
family history of diabetes, those who have given birth to a baby weighing
more than ten pounds, those who have had multiple spontaneous abortions,
those who have given birth to infants with multiple congenital anomalies,
and those 20% above ideal body weight prior to the pregnancy.

9. Socioeconomic Impact

The principal purpose of the socioeconomic impact report is to
stimulate an awareness of the socioeconomic problems in this country as
they relate to diabetes mellitus and to encourage institutional and
community change so as to improve health outcome. Certain socioeconomic
issues which affect the quality of health care for diabetics have been
identified and addressed. These issues include the following:

- Interaction of the individual (patient) with his
  environment: the interventions in health care,
  and their/his outcome.

- Individual behavior as a function of understanding of the disease.

- Other factors such as adolescence, rural life, and non-English-speaking populations.

- Groups with outstanding socioeconomic problems such as the urban and rural poor, the aged, and the institutionalized.

The prevalence rates and mortality rates are one-third higher in non-whites than in whites. Certainly an explanation of this is in order, and it is hoped that through our long-term study we will understand the mechanism here more significantly.

10. Economic Impact

Diabetes is an increasingly important public health problem. The annual cost of diabetes to the United States economy in 1967 was estimated to be $2 billion. The current estimate, excluding the impact of complications, is $5.34 billion, more than double the amount of 1967. This total should be considered a minimal figure because of the difficulty in estimating the impact of complications of the disease. The true cost may well be much higher; hence, elimination of diabetes represents a significant potential benefit to the economy. The cost of eventually eliminating diabetes must be measured so that a judgment can be made as to how much of that expenditure should be provided by public funding.

11. National Diabetes Registry

It became very apparent to all the members of our committee in the process of attempting to gather the information needed for our report that, while a National Diabetes Registry is not feasible at this time, there has been an inadequate reporting system for diabetes. Because of this, a major outgrowth of our committee was the establishment of a free-standing workgroup to address the development of a national diabetes data system. Our epidemiology workgroup collaborated closely with this new workgroup in formulating recommendations for the health and vital statistics data collection and reporting (which form only a portion of the total recommendations of the workgroup on the National Systems for Diabetes Data Resources).

In particular, the committee strongly recommends the revision of the Diabetes Source Book. A National Diabetes Data Council should immediately address the task of developing guidelines for information to be included in the new book which should be available within six to twelve months, and with subsequent volumes every five years. Rather than accumulate and present data, the data council should direct the data to the purpose it will serve, e.g., planning of services, patient counseling, national priority setting, etc. The primary effort will

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emphasize data needs and improvement for implementation to gather the
data for the next edition.

12. Proposed Protocol

We have briefly summarized the problems under each of the categories
delineated under the Scope of diabetes. The specific details in each of
these categories will be found in the body of the individual workgroup
reports, as well as in specific research protocols delineated later in this
report. It would appear, however, that the type of research needed most
under the Scope area is that which could provide important genetic and
epidemiologic data which could be correlated with the more precise studies
of morbidity set up by the Etiology and Pathogenesis Committee. We are,
therefore, proposing that the Committee design a long-term multifaceted
protocol for a comprehensive study of diabetes in a community.

PROJECT TITLE:

The causes and effects of diabetes in the general population.

BRIEF DESCRIPTION OF THE PROJECT:

In a general population of approximately 100,000 persons, subjects
with diabetes (known and occult), those with varying degrees of glucose
tolerance, and a subsample of those with normal glucose tolerance will be
studied. Each group will be examined for baseline characteristics,
including age, height, weight, indices of adiposity, serum lipids, blood
pressure, smoking, insulin levels and diet; for indices of vascular status
(including EKG's and peripheral vascular parameters); and for micro-
vascular disease (including retinal and renal examinations). Also, in a
subsample, the status of glucose tolerance and adiposity of close rela-
tives will be examined. Certain examinations will be repeated periodically
on a long-term basis. A by-product of this study would be the potential
for related basic and clinical investigations.

KEY EVENTS CRITICAL TO THE SUCCESS OF PROJECT:

   1. Identification of a suitable population, resources, and
       personnel.

   2. Formulation of a detailed protocol for each of the
       elements of study.

   3. Assurance of stable long-term funding.

PRESENT STATUS:

Only the present studies of the Pima Indians are in any way compara-
ble in scope and character to the proposed project. Because of the size
and character of the population samples proposed, the findings will yield
information more broadly applicable to the general population.

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INPUT REQUIRED:

Adequate long-term funding, high degree of community cooperation, and a stable team of well qualified investigators and supporting personnel. Estimated cost of $1.5 million per year over a minimum of ten years.

FORM OF RESULTS:

New knowledge on epidemiology, etiology, natural history, and impact of diabetes and its complications.

OTHER FACTORS:

Rather than devising a protocol with a single city or a single community, a similar type of protocol could be developed utilizing a cooperative study in which the new type diabetes centers collaborate in a cooperative long-term study.

13. Concluding Comments

The Committee on Scope and Impact also is concerned about the specific channels whereby its recommendations may be implemented. Because of the many demands that are placed on all of the federal agenices associated with health and welfare, we believe it is unlikely that the goals recommended here, and the goals recommended by the other committees, can be obtained without additional funds and personnel being earmarked for our programs. Therefore, the Committee on Scope and Impact urges that a specific committee, with already well-defined interests and knowledge in diabetes, be set up to see that our recommendations are adequately implemented. Furthermore, we feel that it is essential to devise a method whereby a specific government agency accepting one of the recommended missions (and allocated funding for the mission) is not forced simultaneously to reduce funding or position ceilings for another mission of that agency in order to carry out the mission of our program without additional overall funding or allocation of additional positions.

A complete list (to this time) of all projects recommended by the Committee on Scope and Impact is presented next, followed by a highlighting of the priority recommendations from each workgroup.

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RECOMMENDATIONS FOR PROJECTS, COMMITTEE ON SCOPE AND IMPACT
(in order, by workgroups)

The following is a complete list (to this time) of projects recommended by the workgroups of the Committee on Scope and Impact. Project summary sheets, which outline each project in detail, appear as a part of the individual workgroup reports.

EPIDEMIOLOGY

1. National Diabetes Data Council

2. Guidelines for Diabetes Source Book

3. Health Statistic Data Libary

4. Diabetes Mortality Statistics

5. Death Certificate Linkage

6. Age and Diagnostic Standards for Diabetes

7. Early Treatment of Asymptomatic Diabetes

8. Improving the Outcome of the Asymptomatic Diabetic Pregnancy

9. Causes and Effects of Diabetes in the General Population

MORTALITY

10. Death Certificate Linkage Study

11. Use of Death Certificates in Obtaining Supplementary Information on Selected Diagnosed Disease

12. Medical and Post-Graduate Training on Death Certificate

13. Comparison of Residence on Death Certificate with Actual Place of Residence at Time of Death

14. Multiple Cause of Death Statistics

15. Nationwide Multiple Cause of Death Classification System

16. Problems in Classifying and Selecting Diabetes as a Cause of Death

17. Recording "Age at First Diagnosis" on Death Certificates

18. Biometric Model to Delineate Relative Contribution of Diabetes in Competition with Other Major Diseases

19. Assessment of Rising Diabetes Mortality in Old Ages

MORBIDITY

20. Effect of Treatment on Morbidity in Diabetes

21. Study of Gangrene as a Health Program in a Whole Community

22. Relationships of Glucose Tolerance, Adiposity, Serum Triglycerides, Vascular Disease, Genetics, Diet and Environment in a Whole Population or Representative Sample Thereof

23. World Health Organization Multi-National Study in Vascular Manifestations of Diabetes

24. Epidemiology of Adiposity in a Whole Community

GENETICS

25. Existence of Glucose Intolerance in the Carrier State of Certain Recessive Syndromes

26. Twin Study of the Co-Twin Control Type

27. Population Study to Determine Frequency of Certain Primary Abnormalities in Diabetes Within Each Population Group

PREGNANCY

28. Prevalence Rate for Diabetes in Pregnancy

29. Indications for Glucose Tolerance Testing in Pregnancy

30. Maternal Mortality in Diabetes

31. Risk Factors Relevant to Pregnancy in Diabetic Women

32. Diabetic Retinopathy in Pregnancy

33. Decidual Vascular Structure in Diabetic Women

34. Cellularity of Placentas in Diabetic and Normal Women

35. Adaption of Human Maternal Pancreas to Pregnancy

36. Congenital Malformations in the Child of the Diabetic

37. Insulin Treatment of Gestational Diabetes

38. Natural History of Gestational Diabetes

39. Cardiovascular Disease in Evolving Diabetics

ECONOMIC IMPACT

40. Economic Impact of Diabetes, Including Complications of the Disease

41. A Cost-Benefit Analysis of Current and Future Programs

C. PRIORITY RECOMMENDATIONS: SCOPE AND IMPACT COMMITTEE

The research needs outlined, numbering 41, have been carefully reviewed from the viewpoint of immediacy as well as practicality.

Each of the projects listed is urgently needed. However, it is not realistic to believe that there is funding or manpower for all to be accomplished simultaneously with existing resources. Each of the Scope workgroups was therefore asked to identify the most emergent needs for which resources are now available except for funding. With this stipulation and with priorities set only within individual workgroups, the projects listed in the following table were selected.

In all instances, the projects selected for this priority list involve long-term multifaceted progressive studies in diabetes which depend primarily on assurance of funding for the necessary time periods. If implemented, these projects could yield a cohort of individuals to assess the new discoveries and areas of concern which would surely emerge out of such studies.

The need for many of these projects has existed for 20 or more years. In light of the current lack of knowledge about many facets of diabetes—including the inability to assess adequately its treatment and causes—it is important to give high priority to long-term assured funding for these kinds of studies.

Relevant project summary sheets and other communication (Exhibits 3-11) from the workgroups follow the tables.

PRIORITY RECOMMENDATIONS: SCOPE AND IMPACT COMMITTEE

Title and Purpose	Site and/or Coordinating Agency	Time Period
1. Epidemiology		
Priority # 1		
Establishment of legislated position and support staff to foster, promote, and conduct Epidemiologic studies and manpower development and utilization using Direct, Contract, and Extramural Grant programs.	NIAMDD	
Priority # 2		
a. Causes and Effects of Diabetes in General Population (Multi-Disciplinary: Projects 6 + 9 + 27)	Extramural NIAMDD	
b. National Diabetes Data Group Establishment (by legislation)of a Data Group to promote appropriate data collection and dissemination: (Project #1 and #2 includes publishing of Source Book every 5 years)	National Comm. for Vital and Health Statistics and NCHS	
c. Manpower Development Fellowship (see Etiology and Pathology)	NIAMDD	
Research Career Investigators (RCDA). 2/year for 5 years awarded for 5 years @ $50,000/year each for 10 Total @ $250,000 each		
Post Doctoral Fellowships 4 in lst year; 8 in 2nd; 12 in 3rd; 16 in 4th; 5 in 5th and each year subsequently @ $30,000/year each (salary and institutional costs)		
Priority # 3		
a. Health Statistics Data Library (Project #3)	NCHS	
b. Diabetes Mortality Statistics (Project #14)	NCHS	
c. Death Certificate Linkage (not restricted to Diabetes...only nominal funding included - Project #5 and !0)	NCHS +: NIAMDD-NHLI +NEI +NCI, etc.etc.	

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PRIORITY RECOMMENDATIONS (CONT.)

Title and Purpose	Site and/or Coordinating Agency	Time Period
2. Mortality		
I. Demonstration Project A:		
a. Recording diabetes on death certificates for all those who have diagnosed diabetes at time of death.	NCHS & State Health Depts. of States selected for participation	1 yr.
II. Demonstration Project B:		
Multiple Cause Mortality Reporting System: ACME	NCHS State Health Depts. for all 50 States	3 yrs.
III. Research Project		
a. New criteria and guidelines for classification of diseases and selection of diabetes as underlying or contributory cause of death.	NCHS & 2 Universities & 2 State Health Depts.	3 yrs.
b. Relative contribution of diabetes as cause of death in competition with other associated conditions; what conditions are caused by diabetes?		
c. Survival functions of diabetes with complications and that of counterparts without complications.		
IV. Educational Project (could be included with Education, i.e. Med. Schools, etc.)	School Accredition or U.S. Dept. of Education or AMA or Hosp. Accred. or ?	5 yrs.
a. Training of medical, osteopathic students and postgraduate physicians regarding cause of death certification.		
b. Training of funeral directors regarding allocation of the residence of the diseased.		

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PRIORITY RECOMMENDATIONS (CONT.)

	Title and Purpose	Site and/or Coordinating Agency	Time Period
3. Morbidity	Multiclinical Trial on the Effect of Therapy on Morbidity of Diabetes (See accompanying sheet)	NIAMDD NHLI NEI NICHHD NINDS	7 yrs. or alt. 10 yrs.
4. Pregnancy	Collaborative Multi-Center Trail of Insulin Treatment of Gestational Diabetes to Reduce Perinatal Morbidity and Mortality. Concurrent documentation of Pregnancy Outcome among Overt Diabetics and Controls with Related Treatment and Risk Factors.	NICHHD 6 different Centers	5 yr.
5. Genetics	A. Glucose Tolerance Syndrome (Project 25) Twin Studies (Project 26)	NIAMDD	5 yrs. 5 yrs.
	Misc. studies e.g. HLA,	NIGMS	5 yrs.
	B. Manpower Development Post Doctoral Fellow -1 yr @ 30,000	NIGMS	
	RCDA 1/5 years @ 50,000		
6. Economic Impact	Cost/Benefit Analysis of Current and Future Programs (Three concurrent Task Forces (1 Economist, 1 Physician and 1 Statistician plus 1 Research Assistant and 1 Secretary each)	NIAMDD + 2 University Centers	3 yrs. each @ 200,000 each year

TOTAL DOLLARS FOR SCOPE COMMITTEE

EXHIBIT 3

PROJECT SUMMARY SHEET --Priority Recommendation

PROJECT TITLE: AGE AND DIAGNOSTIC STANDARDS FOR DIABETES

OBJECTIVE: To define normative standards for the glucose tolerance
                 test and to define in quantitative terms the effect of
                 such variables as aging, obesity, dietary factors, and
                 activity levels on the natural history of the develop-
                 ment of diabetes in the population.

APPROACH TITLE:

   A long-term longitudinal multi-disciplinary study to define normative
   age-adjusted diagnostic standards for diabetes.

DESCRIPTION OF PROJECT:

   Cohorts covering the entire age range and both sexes will be selected
   so as to provide appropriate numbers of subjects in the borderline
   range of glucose tolerance along with appropriate controls. Subjects
   will agree to participate in a long-term (10-15 year) longitudinal
   study with periodic testing for diabetes and for the known "end-
   points" of the diabetic state, the micro- and macro-angiopathies.
   Variables known or suspected to have an impact on the development of
   the disease or its complications (obesity, diet, activity, etc.) will
   be assessed.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Identification of principal investigator and institution to pro-
       vide continuity over a 10-15 year period.
   2. Assurance of long-term funding.
   3. Selection of stable population.
   4. Assembly of multi-disciplinary team to measure and evaluate the
       progression and outcome.

PRESENT STATUS:

   1. Extensive background in the technical complexities of glucose
       tolerance testing is available.
   2. Experience in unique problems of the conduct of longitudinal

studies has been gained.
3. Noninvasive quantitative techniques for the assessment of the
   clinical endpoints of the diabetic state have been developed
   (e.g., retinal photography, basement membrane thickness, renal
   function, exercise electrocardiography).

INPUT REQUIRED:

Scientific, administrative, and technical staff for a large scale
multi-disciplinary population study must be developed. Population
base must be selected from among a variety of possibilities (exten-
sion of current longitudinal studies, veterans hospitals, armed
services, employees of large companies, health plan enrollees, etc.)

FORM OF RESULTS:

Computer-based data storage system will provide direct actuarial
analyses (e.g., mortality rates of specific age groups with varying
glucose tolerance characteristics and similar data for morbidity
rates of the diabetes-linked angiopathies). In addition, the inter-
actions of such "risk-factor" variables as age, obesity, dietary
characteristics, activity levels, and metabolic and endocrine factors
in the development of the overt diabetic state will be quantified.

EXHIBIT 4

PROJECT SUMMARY SHEET --Priority Recommendation

PROJECT TITLE: THE CAUSES AND EFFECTS OF DIABETES IN THE GENERAL
                 POPULATION

OBJECTIVE: To achieve understanding of etiology, natural history of
                 diabetes, and its vascular complications.

APPROACH TITLE:

   Comprehensive multifaceted study in a community of diabetes and its
   complications, and of factors relating thereto.

DESCRIPTION OF PROJECT:

   In a general population of approximately 100,000 persons, subjects
   with diabetes (known and occult), those with varying degrees of glu-
   cose tolerance, and a subsample of those with normal glucose toler-
   ance will be studied. Each group will be examined for baseline
   characteristics including: age, height, weight, indices of adipos-
   ity, serum lipids, blood pressure, smoking, insulin levels, diet,
   indices of vascular status, including EKG's, peripheral vascular
   parameters, and microvascular disease, including retinal and renal
   examinations, and in subsamples status of glucose tolerance and
   adiposity of close relatives. Certain examinations will be repeated
   periodically on a long-term basis. A byproduct of this study would
   be the potentiality for related basic and clinical investigations.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Identification of suitable population, resources and personnel.
   2. Draw up detailed protocol for each of various elements of study.
   3. Assurance of long-term stable funding.

PRESENT STATUS:

   Only the present studies of the Pima Indians are in any way compar-
   able in scope and character to the proposed project. Because of the
   size and character of the population samples proposed, the findings
   would yield information more broadly applicable to the general
   population.

<u>INPUT REQUIRED</u>:

   Adequate long-term funding, high degree of community cooperation and
   a stable team of well-qualified investigators and supporting person-
   nel. Estimated cost of $1.5 million per year over minimum of ten
   years.

<u>FORM OF RESULTS</u>:

   New knowledge on epidemiology, etiology and natural history and
   impact of diabetes and its complications.

EXHIBIT 5

WORKGROUP ON MORTALITY

PRIORITY RECOMMENDATIONS

I. Demonstration Project: A

Title   (a)   Recording diabetes on death certificates for all those who have diagnosed diabetes at the time of death.

Title   (b)   Recording age at first diagnosis of diabetes on death certificates.

       Site: Selected states to participate/state health departments

       Coordinating Agency: National Center for Health Statistics

       Time: One-year period; 1976-77

       Cost: $100,000 per state $300,000 for three states

II. Demonstration Project: B

Title   Multiple Cause Mortality Reporting System: ACME

       Site: All states to participate/state health departments

       Coordinating Agency: National Center for Health Statistics

       Time: Three-year period; 1976-1979

       Cost: ($100,000 for NCHS/year; $1,000,000 for 50 states/year
              (
              ($300,000 for NCHS/3 years; $3,000,000 for 50 states/3 year

III. Research Project

Title   (a)   New criteria and guidelines for classification of diseases and selection of diabetes as underlying or contributory cause of death.

Title   (b)   Relative contribution of diabetes as cause of death in competition with other associated conditions; what conditions are caused by diabetes?

Title   (c)   Survival functions of diabetes with complications and that of counterparts without complications.

Title   (d)   Rising diabetes death rate in old ages

       Site: Selected universities (2) and state health departments (2) to participate

       Coordinating Agency: National Center for Health Statistics

       Time: Three-year period; 1976-1979

       Cost: $400,000 per year; $1,200,000 for three-year period

IV. Educational Projects

Title (a) Training of medical, osteopathic students and postgraduate
             physicians regarding cause of death certification.

Title (b) Training of funeral directors regarding allocation of
             residence of the deceased.

Site: (All medical and osteopathic schools in the U.S.
      (
      (All national, state, and local medical and
      (osteopathic associations
      (
      (All funeral directors associations in the U.S.

Coordinating agency: American Medical Association
                      American Osteopathic Medical Association
                      Various Funeral Directors' Associations
                      Conference of Funeral Service Examining
                         Boards of the U.S.

Time: Five-year period; 1976-1981

Cost: $300,000 per year   - $1,500,000 for five-year period

By: Dr. George K. Tokuhata
10-8-75

ns:lb

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EXHIBIT 6

PROJECT SUMMARY SHEET -- PRIORITY RECOMMENDATION

PROJECT TITLE: EFFECT OF TREATMENT ON MORBIDITY IN DIABETES

OBJECTIVE: To determine the effect of metabolic control on the vascular
complications of diabetic patients.

APPROACH TITLE:

A long-term prospective multi-clinic trial on the effects of therapy
on morbidity of diabetes.

DESCRIPTION OF PROJECT:

Patients with insulin-dependent diabetes have early onset of degenera-
tive complications leading frequently to early death. Ten years
after the onset of juvenile diabetes, Knowles found the following
pathology: retinopathy in 64%, proteinuria in 33%, calcification
in 27%, hypertension in 28%, neuropathy in 35%, and cataracts in 47%.

If present methods of therapeutic intervention are useful, it should
be possible to document this fact in a relatively brief period of
10 years or less of observation.

After careful explanation an informed consent patient will be
randomly allocated to a routine treatment or a "tight control"
treatment group. Multiple clinics having the capability of
following between 100 and 150 patients on a long-term basis will
be selected.

Routine treatment will consist of therapy as it is now generally
practiced in the community with dietary instruction and insulin
therapy once or twice daily. This will probably be carried out
under the total care of the primary physician with occasional
consultation at the clinic in order to document progress. Patients
assigned to "tight control" will have all known risk factors for
vascular disease identified and eliminated or treated. This will
include weight, cholesterol, and triglyceride normalization by
dietary means, correction of existing hypertension, control of
blood glucose by both dietary and insulin therapy. Insulin will
be given twice or more times daily to control blood glucose
below 160%mg two hours after the morning and mid-day meal.

Studies will be conducted of the major inpoints of retinopathy, coronary heart disease, peripheral vascular disease, nephropathy, neuropathy, blood pressure, and mortality.

Every attempt will be made to document the population screened for selected study patients so as to approach as closely as possible a 'total population' study.

KEY EVENTS CRITICAL TO THE
SUCCESS OF THIS PROJECT:

1. Identification of an institute and principal investigators to provide continuity over 10 to 12 year period.
2. Assurance of long-term funding.
3. Identification of a loyal and stable population that can be followed for that period of time.
4. Assembly of a multi-disciplined and to some degree, inter-changeable team to measure and evaluate the progress of the research and the eventual outcome.

PRESENT STATUS:

There is a great deal of knowledge now available on the conduct of longitudinal studies and the experience of university diabetes programs is invaluable in establishing a study of this complexity. Extensive background in the technical complexities of controlling endpoint determinations has been developed.

INPUT REQUIRED:

No unique or unusual qualifications are required for this study that have not already been worked out. The most important single requirement is a well-disciplined control center for accumulation of data and for a modicum of results on an ongoing manner.

Cost for a total population of 3,000 patients studied over a 12-year period (two years recruitment and 10 years of follow-up) would be approximately 1.3 million per year.

FORM OF RESULTS:

Results will be analyzed at six-month intervals for all endpoints to be certain that there is no significant difference between results of any two points of therapy. Evidence of significant difference between two points of therapy would be reason for conclusion of the study on the basis of the attainment of the research.

EXHIBIT 7

WORKGROUP ON PREGNANCY -- PRIORITY RECOMMENDATION

Project:

    Institutes a five-year collaborative multi-center trial of Insulin treatment of gestational diabetes for reducing perinatal morbidity and mortality.

    Concurrently, document pregnancy outcome among overt diabetics and controls with related treatment and risk factor.

Coordinating Agency: National Institute for Childhood Health and Development

Time and Cost: First year funding, $900,000

                 Spread out over five years

Dictated by Dr. O'Sullivan
os:lb
10-10-75

EXHIBIT 8

PROJECT SUMMARY SHEET--Priority Recommendation

PROJECT TITLE: ASCERTAIN THE EXISTENCE OF GLUCOSE INTOLERANCE IN THE
                 CARRIER STATE OF CERTAIN RECESSIVE SYNDROMES.

OBJECTIVE: To determine the pathogenesis of glucose intolerance.

APPROACH TITLE:

   The study of glucose intolerance in specific genetic syndromes
   associated with glucose intolerance.

DESCRIPTION OF PROJECT:

   Persons with certain genetic syndromes will be evaluated using the
   oral glucose tolerance tests to determine the presence or absence of
   glucose intolerance.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Identification of specific genetic syndromes.
   2. Well controlled oral glucose tolerance tests.
   3. Matching these results in similar group of patients without the
       genetic syndrome.

PRESENT STATUS:

   No current studies of this type are being done.

INPUT REQUIRED:

   Identification of appropriate patient groups.

FORM OF RESULTS:

   The identification of specific genetic syndromes associated with
   glucose intolerance.

EXHIBIT 9

<u>PROJECT SUMMARY SHEET</u> --PRIORITY RECOMMENDATIO

<u>PROJECT TITLE</u>: TWIN STUDY OF THE CO-TWIN CONTROL TYPE.

<u>OBJECTIVE</u>:   The study of diabetes mellitus in concordant and dis-
cordant monozygotic twins.

<u>APPROACH TITLE</u>:

Same

<u>DESCRIPTION OF PROJECT</u>:

Identify concordant and discordant monozygotic twins at various
ages in an attempt to identify different types of diabetes.

<u>KEY EVENTS CRITICAL TO THE
SUCCESS OF PROJECT</u>:

1. Identification of concordant and discordant monozygotic twins.
2. Perform FBS or OGTT when indicated.
3. Correlate this with age and other related factors.
4. Determine specific patterns diabetic development.

<u>PRESENT STATUS</u>:

A minimal amount of current knowledge is available in this field.

<u>INPUT REQUIRED</u>:

See above.

<u>FORM OF RESULTS</u>:

Results will be presented as cross sectional study of the subjects
involved.

EXHIBIT 10

PROJECT SUMMARY SHEET --PRIORITY RECOMMENDATION

PROJECT TITLE: POPULATION STUDY TO DETERMINE THE FREQUENCY OF CERTAIN
                 PRIMARY ABNORMALITIES IN DIABETES WITHIN EACH POPULATION
                 GROUP.

OBJECTIVE: To ascertain the frequency of the various abnormalities
                 in diabetes.

APPROACH TITLE:

   Population study to determine the frequency of certain primary
   abnormalities in diabetes within each population group.

DESCRIPTION OF PROJECT:

   Examine each population group and obtain the data required to test
   specific modes of inheritance.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Identify population groups.
   2. Analysis of various abnormalities in diabetic population of
       each group.

PRESENT STATUS:

   Several limited studies have been done in the past with inconclusive
   results.

INPUT REQUIRED:

   See above.

FORM OF RESULTS:

   Results will be age, population and abnormality specific for
   diabetes.

II. Report of the

WORKGROUP ON

DEFINITION AND DIAGNOSIS OF DIABETES MELLITUS

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

Thaddeus E. Prout, M.D.

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II. REPORT OF THE WORKGROUP ON
DEFINITION AND DIAGNOSIS OF DIABETES MELLITUS

A. INTRODUCTION

A monumental task has been accomplished in a few months through the efforts of dedicated people who have here compiled an authentic reference to the state of our knowledge of diabetes mellitus at the end of 1975. No one has attempted before to review on this scale and under these circumstances the entire scope of diabetes, the research needed on it, and the efforts in patient education and treatment. Implicit in this type of review is the difficulty of summarizing general studies and of establishing and appraising the magnitude of the problem at this time without elisions, contractions, and editorial shortcuts. In the following pages, thorough reference information has been given for each author's work which is freely quoted. Apparent discrepancies may appear as a result of the use of data from different sources by different authors. In all instances, reference to the original article should be made for technical detail and for establishing more specifically the exact results reported by the author in the context in which he meant them to be taken.

Underlying the entire discussion are the criteria for the diagnosis of diabetes. To say that these diagnostic criteria are exact and equally applicable to all of the many authors quoted is untenable. To establish de novo a definition of diabetes which can be applied retrospectively to all studies is impossible. However, it is necessary to begin this discussion with a definition of diabetes as the term is now generally applied.

B. DEFINITION OF DIABETES

Definition of the problems of diabetes can paradoxically be frustrated by attempts to answer the question "What is diabetes?" Parts of the definition are easily stated, others are clouded by uncertainty and lack of reliable information, and still others are beginning to assert their preeminence but are as yet undefined. An easily stated, usually acceptable assertion about diabetes is that it is a complex metabolic derangement, characterized by relative or absolute insulin deficiency. More information is still needed about the surmise that this deficiency

is usually or frequently accompanied by microvascular and macrovascular pathology, unique in part, and in part merely an accelerated process of aging.

And in an area of definition not yet sufficiently explored and delineated but nonetheless essential for our consideration, the possible primary roles of glucagon and somatostatin, among others, cannot be ignored in the attempts to define diabetes. Thus, the present state of medical science does not permit a succinct definition satisfactory to everyone.

The clinical definition of the diabetic state continues to be stated in terms of the alteration in glucose tolerance. This has been also hampered in the past by insistence that all patients above a stated level of glucose tolerance are "diabetic" and all patients below this level are normal. Clearer clinical definitions of diabetes, including acceptance of a "borderline" state, are needed. Fundamental principles, such as the effect of aging itself on glucose tolerance, likely to be ignored in earlier studies, must now be recognized. One of our first efforts will therefore be given to a definition of the clinical spectrum of carbohydrate intolerance.

C. DIAGNOSIS OF DIABETES

The diagnosis of diabetes, as implied in the definition, is based on the glucose levels of the plasma. Other methods by which the diagnosis is sometimes established will be included as references, but the oral glucose tolerance test remains the method against which other diagnostic criteria are measured. A method is needed which can become a bench mark for the future diagnosis of diabetes, which can be applied to all ethnic groups, and against which newer methods and ideas can be tested. From this description of a method for the standardization and interpretation of the oral glucose tolerance test, it will be possible to derive a basis for population screening which can be universally applied. It will also be possible to derive principles on which to base glucose control. Because of these important and urgent needs, this compendium of present information on diabetes mellitus will begin with a protocol for the use and interpretation of the oral glucose tolerance test as a move to establish uniformity of data collection for the future.

D. STANDARDIZATION OF THE ORAL GLUCOSE TOLERANCE TEST (OGTT)

Adoption of an internationally agreed upon standard oral glucose tolerance test (OGTT) would allow a worldwide exchange of information concerning diabetic patients. Such a standard would, of necessity, be based on arbitrary decisions, but unless they are made, the term

"diabetes" will continue to have different meanings for different investigators. An agreement on a set of standards would be only a first step towards this goal. Definitive criteria of normality and abnormality will have to await the results of longitudinal studies now underway which will attempt to correlate the results of glucose tolerance testing with subsequent pathologic changes.

This chapter will outline the conditions to be observed in performing the OGTT and will attempt to bring into focus a unifying concept for interpretation of the results. It is recommended that greater care be given to the details of testing and that all publications in the future include as much of the actual data on individual patients as is acceptable to editors of journals.

1. INDICATIONS FOR THE OGTT

The physician who decides to perform an OGTT should do so only with a clear understanding of the indications and limitations of the test. Indications for performing an OGTT may be classified as follows:

a. Diagnostic clarification of problems relating specifically to carbohydrate metabolism.

1) Borderline glucose values obtained non-fasting or from screening procedures.

2) Glycosuria in the absence of diagnostic hyperglycemia.

3) Periodic testing of persons with high risk of glucose intolerance, with or without positive screening tests, including studies for gestational diabetes.

4) Initial study of persons with symptoms suggestive of hypoglycemia. This may be a useful clinical tool for defining variations of normality common to the populations of patients presenting themselves with symptoms suggestive to them or to their physicians of hypoglycemia.

   It should be emphasized, however, that definition of true hypoglycemia states related to a fundamental alteration in carbohydrate metabolism is not possible with the OGTT.

5) Unusual, unexplained weight change.

6) Mothers of large babies.

7) Recurrent infections.

8) Obesity (over 20% of standards).

9) Polyuria, polydipsia, polyphagia.

10) Multiple spontaneous abortions and/or birth defects.

b. Further study of a pathologic condition in which a diagnosis of diabetes would be of therapeutic usefulness.

1) Metabolic conditions frequently associated with diabetes (elevated triglycerides, cholesterol, or uric acid).

2) Unexplained presence of neuropathy, retinopathy, peripheral vascular disease, or coronary heart disease.

c. Research Project.

2. CONTRAINDICATIONS TO OGTT

The dangers in performance of the OGTT are very small. Even patients with undiagnosed high blood glucose values who inadvertently are given a loading dose of glucose for testing purposes are unlikely to be harmed. Nevertheless, unnecessary use of the OGTT should be avoided. The OGTT is unnecessary when the fasting plasma glucose is over 130 mg/dl, because this alone, if confirmed, establishes the diagnosis of diabetes.

It should be noted that glucose tolerance testing is rarely indicated in routine clinical practice involving children and youth. The occasional youngster with signs or symptoms suggesting diabetes but with undetermined need for insulin can be evaluated by fasting and post prandial blood glucose determinations. The OGTT is not recommended for diagnosis of "hypoglycemia" or for genetic counseling (for example, testing of siblings) outside of a research setting. Our reasons for concern with glucose tolerance testing in routine clinical practice are:

a. There is a general failure to appreciate or control testing variable that appear more critical in children than in adults. Highly significant effects of time of day, glucose dose, and duration of fasting (both too short and too long) were noted in analyzing several thousand OGTT's done in the relatively controlled setting of a pediatric multiphasic testing program; these variables invalidated much of the data.

b. There is widespread false diagnosis of hyper- and hypoglycemia due to failure to appreciate testing variables and normal variation.

c. This over-diagnosis and even appropriate diagnosis in a few cases
    leads to _stigmatization_ of youngsters with diagnostic labels that
    have no significance for their health planning and can adversely
    affect self-concept.

d. There is little or no advantage to having advance information
    that a youngster has abnormal glucose tolerance. Most such
    patients remain stable indefinitely and the few (less than 10%)
    who go on to overt diabetes are not aided by prior awareness
    of abnormality; there is no therapy to forestall such progres-
    sion.

3. PERFORMANCE OF THE OGTT

The following recommendations are advised for all OGTT's. In testing
for research purposes, they must be rigidly followed. For clinical
testing, conditions are not always ideal. Consequently, tests done under
less than ideal circumstances should be interpreted with caution and may
need to be repeated if the results are at all equivocal.

a. Dietary Preparation

    Carbohydrate intake should be at least 150 grams on each of the
    three days preceding the test. No food or calories in any form
    should be consumed for at least eight hours and for not longer
    than sixteen hours prior to testing. It is important to note
    that water is permitted and, indeed, the state of hydration
    should be reasonably normal.

b. Physical Activity

    The test should be performed on ambulatory patients rather than
    on patients on bed rest or hospitalized for other conditions.
    Minimal walking about during the test may be permitted, but
    undue exercise should be prohibited. In general, patients should
    be seated comfortably during the test. Drinking coffee as well as
    smoking is prohibited. If the patient has been vomiting or has
    significant nausea, the test should preferably be postponed.
    Vomiting of the glucose load invalidates the test.

c. State of Health and Other Chemical Conditions

    In general, a period of at least two weeks of good health is
    desirable before the test. Tests done under conditions known to
    alter glucose tolerance tests (e.g., endocrinopathies or
    pregnancy, post sub-total gastectomy, etc.) may provide useful
    diagnostic and prognostic clinical information. Any abnormal or

equivocal tests should be if possible repeated, however, after
return to normal in order to obtain a reliable assessment of the
state of carbohydrate metabolism in the unstressed state.

d. Drugs Altering OGTT

These include many of the common drugs such as diuretics, oral
contraceptive agents, and the salicylates. This subject is
discussed more fully in the original reference. (See Standardi-
zation of OGTT.) All medications that are not essential should
be discontinued at an appropriate interval (depending on drug
disappearance rate) prior to testing. Oral hypoglycemic agents
should be discontinued for at least two weeks prior to testing.
Essential medications will have to be taken, of course, and
insofar as this represents the permanent physiologic state of
the patient, test results can be given approximate interpretation
for clinical purposes.

e. Time of Testing

Glucose tolerance decreases later in the day, and therefore, in
order to apply obtained values to normative standard, tests
should be done in the morning.

f. Size of the Glucose Load

The size of the glucose load is theoretically the most important
determinant of the glucose tolerance test, but little difference
may be seen in tolerance following glucose loads that vary from
50 to 100 g. (Boshell, et al.). Nevertheless an international
standard is greatly to be desired. Unfortunately, there is no
agreed-upon standard load -- and little definitive information
on which to base a decision. Past glucose tolerance data are
based on glucose loads varying from a 50 g. dose to a dose of
1.75 g./Kg of ideal body weight usually given as a 25% solution.
In many clinics, a 75 g. dose of a premeasured commercial
preparation is preferred. A standard glucose dose of 40
grams/M^2 diluted to a volume of 300 ml and consumed in five
minutes has been recommended. (See Standardization of Use,
OGTT). For a hypothetical patient 5' 8" tall, 165 lbs. in
weight, the following approximations of the loading dose can
be made, based on the various recommendations.

1.75 g./Kg IBW	= 125 g. Glucose
100 g. Standard	= 100 g. Glucose
40 g./M^2	= 75 g. Glucose
1 g./Kg	= 75 g. Glucose
Commercial Preparation	= 75 g. Glucose

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Until a standard loading dose of glucose is agreed upon, the fixed 75 g. dose for adults and 1 g./lb. to a maximum dose of 75 g. for children is recommended. This is the most convenient and widely used glucose load, and available information suggests that data derived from the larger loading doses are generally interchangeable with the 75 g. dose.

For adults that are well outside of the average body size, some variation in glucose load may be used. For example, patients less than 75 pounds in weight may be given a dose of glucose based on 1 g./lb. body weight as in children. Patients in excess of 250 pounds may be given a standard dose of 100 g. glucose.

g. Sample Times

The fasting, one and two hour samples are recommended for routine use since they yield the most relevant diagnostic information.

h. Preparation and Analysis of Plasma Specimens

Because automated equipment is so widely used, most tests in hospitals and in commercial laboratories are performed on plasma or serum. Variations between the Hoffman ferricyanide method and other "true" glucose techniques (e.g., Somogi-Nelson or glucose oxidase) performed on plasma or serum are considered clinically trivial. Plasma and serum glucose levels are elevated approximately 15% above those obtained from whole blood and vary only slightly with hematocrit changes.

Capillary bloods are obviously convenient under many circumstances, but there is no good method for comparison of these values to the more commonly used venous samples over the entire range of glucose values.

4. REPORTING AND INTERPRETING THE RESULTS OF THE OGTT

The fasting blood glucose is relatively insensitive to age and probably increases only 2 mg. % per decade after the age of thirty (8). In contrast to this, the one-hour glucose has been found by various authors to have an average increase from 6 to 14 mg. % per decade utilizing various test doses of glucose and experimental conditions (7, 2). The average increase for the two-hour value utilizing a glucose load of 1.75 glucose/M^2 has been well studied by Andres and found to be 6 mg. % per decade (2). This investigator has also established a

percentile ranking of glucose values two hours following challenge based upon age.

In a study utilizing a glucose dose 1.75 g./kg (2), a progressive age effect was found. From the data, a nomogram was constructed which related age and the two-hour glucose level to a perceptible rank scale. Thus, an individual's age-adjusted rank could be easily determined. The decision concerning the percentage of the population to be classified as "abnormal" and as "borderline" was an arbitrary one; Andres designates the upper 7% of 70-year-olds as falling into this group. He emphasizes that this is simply a rule of thumb which avoids classification of very large numbers of middle-aged and elderly subjects as diabetics and yet which allows the percentage of abnormalities (and of borderlines deserving close follow-up) to increase with age.

Accounting for both an increase in the normal elevation of post-challenge values with age and a rising prevalence of diabetes of 1% per decade, it has been possible to utilize a nomogram of experimental data to delineate the lower limit of normality (2). Andres also suggested an increase in the prevalence of a borderline state not clearly diagnostic of diabetes of 1% per decade over the age of thirty. In effect, the lower limits of normality from Andres' data establish, by his criteria, a population with some aberration in glucose utilization of 2% per decade for subjects over thirty.

Fajans has also taken account of an increase in blood glucose values after challenge and has recently suggested an increase of 10 mgs. % per decade for the one- and two-hour values for patients after fifty years of age (4). These increments represent an increase given by the previous criteria of Conn and Fajans (5). The basis for this judgment is not yet clear.

With clear evidence that there is an increase in the post-challenge level of plasma glucose with age and no established marker for the upper limits of normality, the diagnosis of diabetes must, of necessity, be based on acceptable assumptions. In establishing these limits, it is essential that the medical profession avoid penalizing older individuals, especially in industry and in relation to medical insurance, by making the diagnosis of diabetes without regard to changes in glucose.

Table 1 shows the currently used values for the diagnosis of diabetes as reported from Fajans (4) and for values derived from Andres (2). These represent the lower and upper bounds respectively for the limits of normality in use at the present time. The values given in their table appear somewhat higher than values customarily used, since glucose values derived from serum or plasma are raised (approximately 15% above whole blood). These values are given in graphic form in Figure 1.

In order to develop a unifying concept between these two points of view, it is first recommended that a <u>lower limit</u> of normality be accepted as adapted from Fajans. There is virtually universal agreement that all persons below this limit are, in fact, normal. The zone between this line and the lower limits adapted from Andres' data is to be designated <u>borderline</u>. This is an area of disagreement between the available data from these two investigators, but this area is readily accepted by most physicians as truly borderline.

A "borderline" group designated by Andres approximately 20 mgs. per decade above the range previously shown is more difficult to compromise. This range is not immediately acceptable by most investigators as "borderline," yet it should be set aside for possible usefulness in the future depending on further confirmation and acceptance of the Andres concept. Designation of this range as "probable diabetes" will allow this group of patients to be the subject of further study in terms of their glucose intolerance over time. It will also preserve its differentiation from the area above this, which is presently accepted by everyone as diagnostic of diabetes.

A similar labeling system is shown in Figure 2 for the "Sum OGTT-2 Hours" but ignoring the designation of "probable diabetes." Difficulties in interpretation of glucose values may arise when only one of the individual values in Table 1 is found in a specific category. This difficulty can be avoided if the Sum OGTT-2 Hours is then used for final arbitration. This is a convenient method for calculating the area "under the curve" and makes diagnostic use of the entire two-hour glucose tolerance curve rather than relying on a single value. Thus, a series of glucose values for a 55-year-old individual would be interpreted as follows (plasma, glucose, mg%):

Fasting	1 Hour	2 Hour	Sum OGTT	Diagnosis
100	210	140	450	Normal
110	220	160	490	Borderline
115	220	170	505	Diabetes

There is a good reason to extend the criteria listed for age 20 back to age 0. Conversely, there is little reason to alter these age-based criteria for the diagnosis of diabetes complicating pregnancy.* It should again be emphasized that a lower renal threshold, the presence or absence of glycosuria, or the occurrence of hypoglycemia in a four- or five-hour OGTT is not useful or relevant to the diagnosis of diabetes. Finally, use of USPHS criteria or other screening systems,

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*See Report of Workgroup on Pregnancy of Scope Report.

particularly those giving greatest weight to fasting and the three-hour plasma glucose value, are clearly not useful in the light of information accumulated since their introduction (16). These methods of diagnosis are not recommended.

The present information as presented is consistent with acceptance of the diagnosis of diabetes on the basis of confirmed fasting plasma glucose levels within the borderline zone. Patients with random blood glucose determination in the borderline zone should be followed up with an OGTT. Further use of terms such as "latent diabetes," "pre-diabetes," and other such terms suggesting a diagnostic significance of a border-line test should be eliminated or at least redefined in terms of the currently used tests until there is additional evidence for their relevance.

A consideration should be made also of repeated tests of glucose tolerance which are variable. Although the tendency in the past has been to judge patients by their worst test, it is more reasonable to attempt a summation judgment based on all of the available data. A useful plan for a decision, based on three tests over an extended time span, might be as follows:

	Test #1	Test #2	Test #3	Final Opinion
Patient A.	Normal	Borderline	Abnormal	Normal
Patient B.	Borderline	Borderline	Normal	Normal
Patient C.	Abnormal	Borderline	Borderline	Borderline
Patient D.	Abnormal	Normal	Normal	Borderline

The final narrative opinion should summarize the total experience. These are examples of opinions which would be interpreted in a different way under other circumstances. For example, one may judge patient "B" to be "Borderline" and subject to additional testing if the patient is in a special risk category or if the "Borderline" tests were done under conditions of stress and had suggested to the physician that the patient had only a very limited carbohydrate tolerance.

5. INTERPRETATION OF OGTT IN CHILDHOOD

Guthrie and others (6) have documented glucose tolerance in 200 normal children with attention to details of preparation, exclusive of patients with a family history of diabetes. A loading dose of 1.75 g. glucose/kg IBW up to a maximum of 100 g. was used. Studies were conducted to compose venous serum samples and capillary blood glucose values as follows:

	CAPILLARY	VENOUS SERUM
Fasting	84± 11 mg/100 ml	87 ± 13 mg/100 ml
Hour	150± 32 mg/100 ml	136 ± mg 100 ml

In spite of the fact that a higher loading dose of glucose was given and capillary blood was used, the values obtained were remarkably similar to normal limits set by the Fajans Criteria for the working one- and two-hour value. As noted elsewhere, there is no precise way to correct for differences between capillary and venous samples and it is therefore recommended that (1) the loading dose for adults less than 75 lbs. (1 g. 1 lb. to total of 75 g.) be adopted for use in children and (2) that criteria for ages less than 30 years be extended to include children. Rosenbloom and Associates (1975) have studied the age group 18 to 132+ months extensively and also correlated the OGTT with the venous insulin levels.

6. OTHER CONSIDERATIONS IN ESTIMATING GLUCOSE TOLERANCE

Other tests have been utilized in the diagnosis of diabetes but are beyond the scope of this brief review. They are (1) the intravenous glucose tolerance test (13, 2), the tolbutamide tolerance test (2), and (3) the cortisone-glucose tolerance test (10). These tests have been used primarily as research tools, or in instances in which a patient who has a normal OGTT presents a complication believed to be related to carbohydrate intolerance. There has been some interest in expressing glucose tolerance in terms of concomitant measures of serum insulin, but the usefulness of this additional determination for diagnostic purposes is not yet clear. The low or flat GTT is defined as one which rises less than 20 mg. % above the fasting level. Such a tolerance curve has no unique physiologic interpretation and is observed in approximately 15-20% of normal adult individuals.

7. SUMMARY

The following points deserve emphasis:

a. Most data being reported today are serum or plasma glucose values and are 15% higher than whole blood glucose determination used heretofore.

b. Glucose levels in plasma at standard times following a glucose load increase with age. A normal plasma glucose at two hours for the seventh decade would be 50 to 75 mg. % higher than the upper limits of normal for an individual in the second decade.

c. Longitudinal studies of the pathology of patients dying at various ages will be needed to make final correlations between glucose tolerance and the disease processes.

d. The formulation of a more precise interpretation of the GTT will answer a need that has not been met in the past (9, 15, 12). The language of the interpretation of the GTT in the future should reflect these concepts. These could include a percentile ranking by age of the two-hour, post-testing serum glucose (5) and interpretation as to whether or not the test is normal, borderline, or abnormal -- based on the "SUM OGTT/2-HRS" and appropriate remarks relating to the need for retesting of patients with borderline results.

e. Screening studies should be based on the same basic principles as the more complete OGTT. In this way, the lack of credibility of the screening program will be eliminated.

f. Discrepancies among tests should be recognized, and the best judgment as to the state of the patient's carbohydrate status should be made on the basis of all the data required.

g. In view of the prejudice, particularly in industry, associated with the diagnostic term "diabetes," use of these criteria will permit the clinician to make the diagnosis of diabetes with greater precision and will not penalize older patients with diagnostic criteria based on a younger population. At the same time, it will allow the physician to introduce therapeutic measures when indicated.

h. Finally, it should be pointed out that in our present state of knowledge and utilizing present methods of therapy, the treatment goals in older patients should be readjusted to reflect the fact that older individuals exhibit higher normal and borderline post-prandial blood sugars than normal, younger individuals.

(See Table 1 and Figures 1-2).

E. USE OF THE OGTT CRITERIA FOR SCREENING

Screening tests for detection of diabetes have been widely criticized as being wasteful of money and resources. This criticism comes largely from the lack of critical definition of what is to be accomplished by this screening process and from faulty criteria for interpretation of the test used. For mass screening, the diagnostic level of the fasting blood glucose could easily be established. Based on the interpretation of the OGTT, all patients below the age of 50 having a fasting plasma glucose above 140 mg. percent should be

TABLE   1
GLUCOSE TOLERANCE WITH AGE

A. Adapted from FAJANS (5)

AGE	FAST	1 HOUR	2 HOURS	SUM OGTT/2 HRS.
-50	110	185	140	435
50-60	110	195	150	455
60-70	110	205	160	475
70-80	110	215	170	495

B. Adapted from ANDRES (2)

AGE	FAST	1 HOUR	2 HOURS	SUM OGTT/2 HRS.
-30	110	185	165 (185) *	460
30-40	112	191	175 (195)	478
40-50	114	197	186 (205)	496
50-60	116	203	195 (215)	514
60-70	120	215	215 (245)	550

* In parentheses are given the approximate values for patients above
normal but not clearly diagnostic of diabetes by the Andres criteria.
In Figure 1, and in the text, this range of values has been designated
"probable diabetes." The data was calculated from the Andres monogram
for whole blood glucose by addition of 15% on plasma glucose and "rounding
off."

C. Adapted from GUTHRIE (Guthrie, et al.,1973)

PERCENTILE	FAST	1 HOUR	2 HOURS	SUM OGTT/2 HRS.
97th	111	172	140	423
90th	99	152	126	377
84th	95	137	119	351

Two hundred children were tested up to 13 years of age. Note that
the area above the 95th percentile (upper 3%) is considered diagnostic
for diabetes. It is recommended that other values not clearly less than
the 90th percentile be considered "borderline." Slight improvement in
tolerance is seen between the 90th and the 84th percentile. Capillary
bloods were used.

Figure 1

DIAGNOSTIC LEVELS OF PLASMA GLUCOSE 2 HOURS AFTER GLUCOSE CHALLENGE FOR VARIOUS AGES
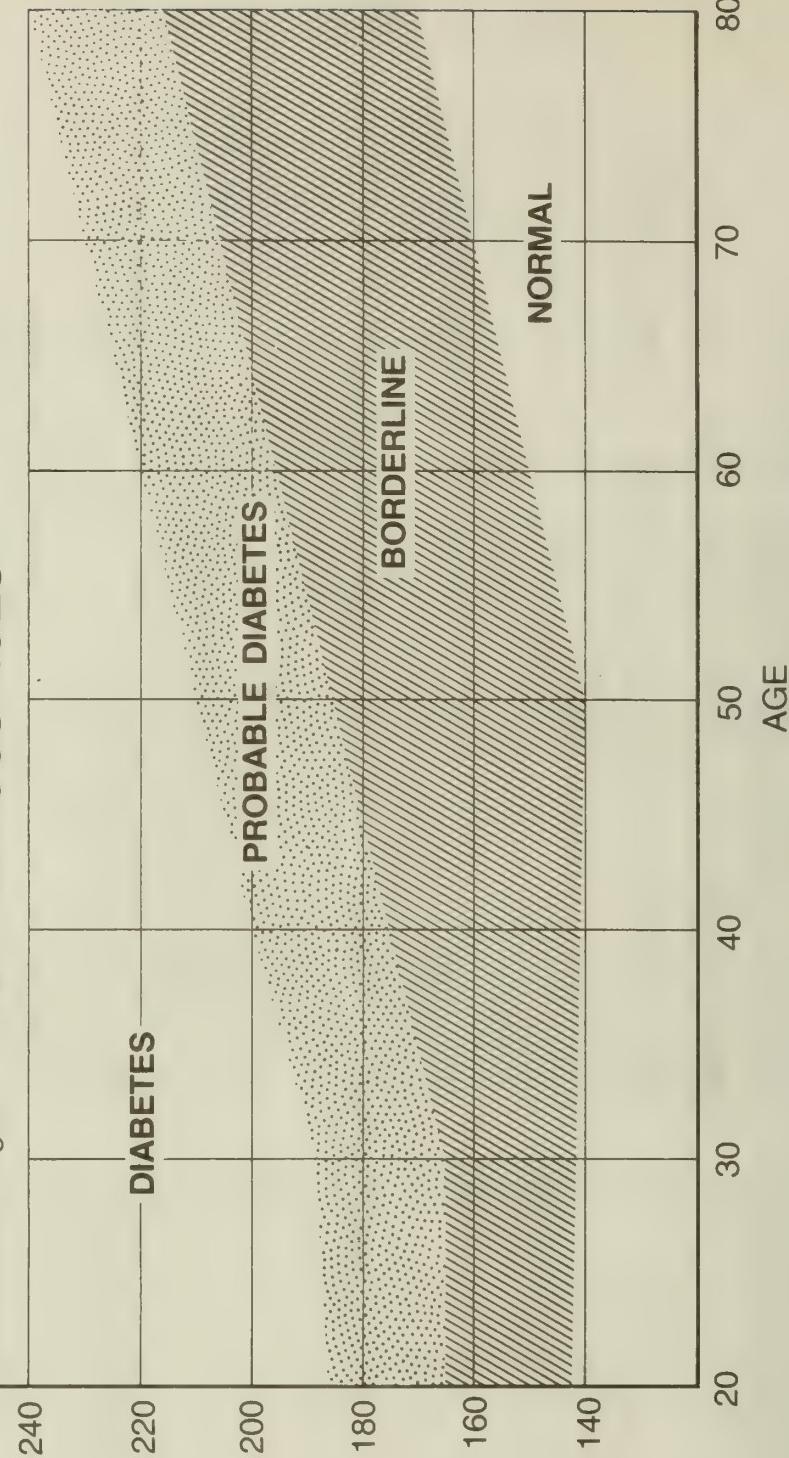
The values drawn are based on information derived
from Fajans and Andres, as shown on Table 1.

Figure 2

DIAGNOSTIC LEVELS OF SUM OGTT/2HR. (F+1+2HR.) AFTER GLUCOSE-CHALLENGE FOR VARIOUS AGES
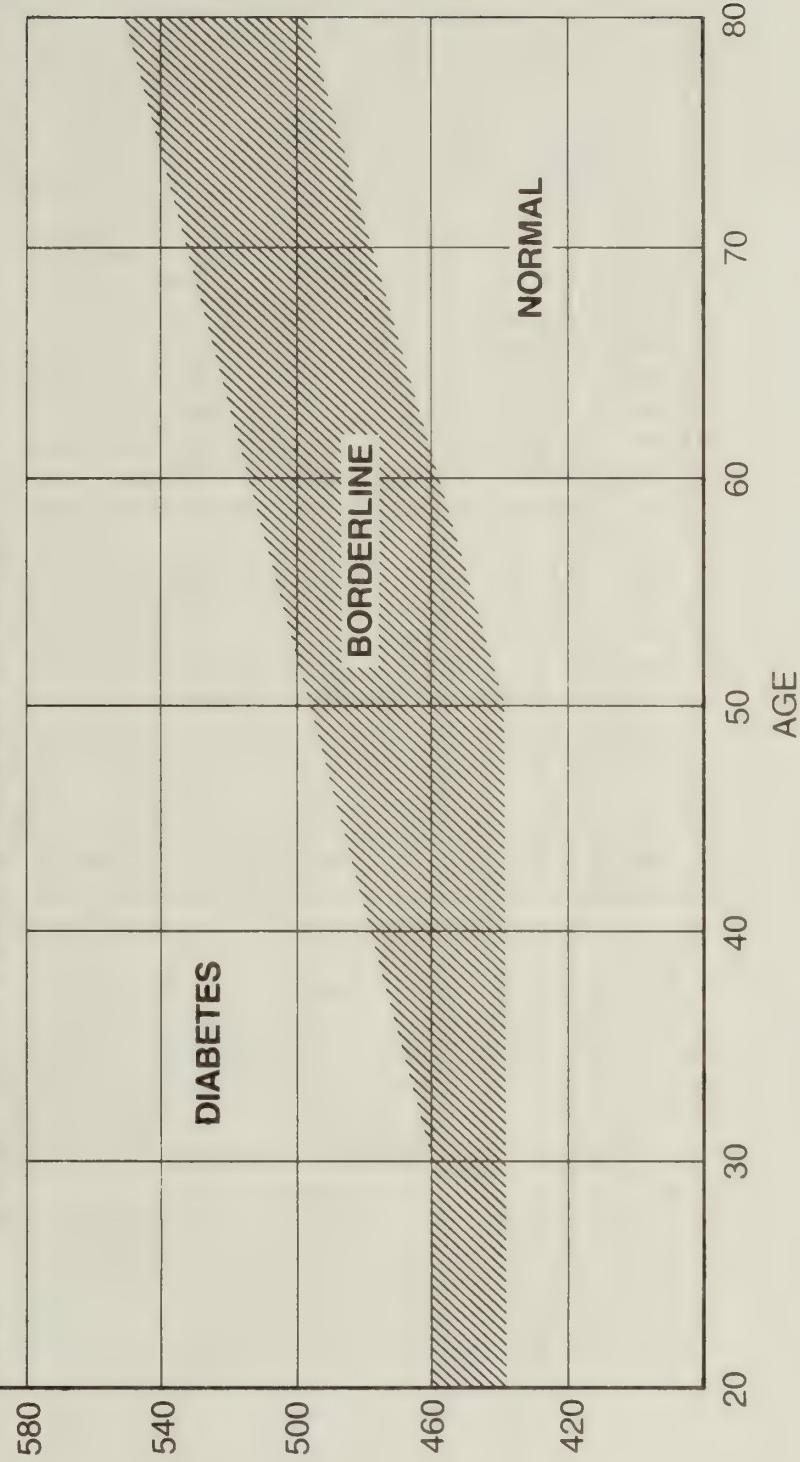
The Sum-OGTT/2 hours is useful in arbitration of equivocal tests. A patient with a single abnormal 1-hour or 2-hours value would be diagnosed on the basis of the total sum of the 2-hour OGTT.

considered diabetic. This level is then raised in accordance with the
levels of normality shown in Figure 2 for the two-hour plasma glucose
following glucose challenge to 150, 160, and 170 mgs. percent at ages 60,
70, and 80 respectively. For practical purposes, the level of 150 mgs.
plasma glucose per 100 ml. is easily remembered and quite acceptable as
a cutoff for the diagnostic level of the fasting blood sugar for all
ages. Under most circumstances, a fasting blood sugar over 130 mg. if
challenged with recommended glucose load would probably have an
abnormally high OGTT. However, it should be noted that the fasting blood
glucose is an extremely insensitive method for early diagnosis of
diabetes, and this is not recommended for screening purposes.

Urine screening tests have been condemned and are generally believed
not to be very useful as screening procedures. On the contray, the
amount of glucose passed in the urine is dependent upon the plasma
glucose and the glomerular filtration rate. Positive urine tests for
glucose in the absence of an altered glomerular filtration rate imply
that glucose has exceeded the "renal threshold" or, more correctly, the
tubular maximum for glucose. Since the tubular maximum for glucose is
not usually exceeded at less than 230 to 250 mgs. plasma glucose in
normal subjects, the presence of glucose in a post-prandial sample
usually implies that these levels have been exceeded. Little additional
information is to be gained by the measurement of the "degree" of
glucosuria since the "concentration" of glucose in the urine is depen-
dent on the state of hydration of the subject. It is clear from this
brief description that a positive urine glucose, in the absence of
altered renal blood flow, is likely to imply diabetes but false
negatives are common. Urine tests are, therefore, of only limited
usefulness as screening procedures.

A screening program based on plasma glucose determinations two
hours after a glucose challenge would be the ideal screening technique.
With this procedure, accumulated data are comparable to those of
similar later tests and also to results of subsequent oral glucose
tolerance tests.

For screening purposes, it is therefore recommended that a 75 mg.
glucose load be administered and a blood glucose determination drawn
two hours later. The interpretation of the two-hour value would then be
based on criteria in Table 1 or Figure 1. The accuracy and relevancy
of the interpretation will depend largely on how closely the screening
test approximates the conditions set for the OGTT. Tests done under
conditions of preparation at various times since the last meal and at
various times during the day will be much less accurate for diagnostic
purposes. It should be noted that most of the conditions that might
be ignored in casual screening procedures would probably lead to false
positive results in a small percentage of patients. False negative
results are more difficult to produce. Since screening procedures are

designed primarily to alert individuals to present or possible future problems, the false positive errors are not necessarily bad.

F. USE OF ORAL GLUCOSE TOLERANCE TEST CRITERIA FOR CONTROL

Establishing criteria for control is one of the most controversial aspects of the treatment of diabetic patients. If diabetes has a "unimodal" distribution within the normal population of the major ethnic groups in Western society, it will not be possible to establish a limit to the plasma glucose above which everyone is diabetic and below which everyone is normal except by arbitrary judgment based on our present state of knowledge.

In the past, the levels of blood glucose set to establish "control" were likewise arbitrary, and based on the mean blood glucose determinations found in the young without regard for the normal increase in blood glucose with aging. Thus, the criterion for the classification of "good control" at the Joslin Clinics (Joslin, 1971) based on whole blood glucose in relation to food has been set as follows: Fasting, 110 mg%, 1 hour p.c., 150; 2 hours p.c., 130; 3 hours p.c., 110.

In a pathologic state characterized by elevated chemistries, it is generally assumed the lower the "variable," the better the condition, but this cannot always be proven.   It would appear that normalization of cholesterol and triglycerides follows this rule as a risk factor for the atherogenesis. The effect of the level of blood glucose as a risk factor for atherogenesis or microvasculopathy is less clear. As pointed out elsewhere (2), there is a normal increase in blood glucose following glucose challenge with the aging process. The clinician should be on firm therapeutic grounds if he does not require lower glucose values of the patient with "diabetes" than can be logically expected from the aging population without diabetes. For these reasons, it is logical to conclude that blood glucose determinations two hours after challenge which fall within the "abnormal" range should be considered "normal." More important, it may be hazardous to insist on "normalizing" blood glucose levels in the aging population to levels based on younger subjects. Patients in the older age group who have had the diagnosis of diabetes established on criteria derived from, and for, a younger population -- and are then subject to glucose "control" through the use of hypoglycemic agents -- are doubly jeopardized.

It is therefore recommended that the same criteria used in the diagnosis of diabetes (presented in detail in the previous section) be applied to the therapeutic goals for treatment. Therapeutic agents are not recommended for patients whose blood glucose determinations fall within the borderline range, given in previous figures. In this approach, the aging population will have therapy based upon what we now know about the normal physiology for their age and not upon criteria established for young patients.

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III. Report of the

WORKGROUP ON

EPIDEMIOLOGY

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

Peter H. Bennett, M.D.

III. REPORT OF THE WORKGROUP ON EPIDEMIOLOGY

A. PREFACE

The Epidemiology Workgroup of the Committee on Scope and Impact of the National Commission on Diabetes was charged with responsibility to review and make recommendations concerning the prevalence and incidence of diabetes in the United States and to document the magnitude of the problem, as this could be perceived through the utilization of morbidity statistics. Additional charges included a review of etiologic factors in diabetes, excluding genetic factors, and recommendations concerning the status and desirability of diabetes case finding. (See also the report of the Committee on Etiology and Pathology.)

It became immediately apparent that the available morbidity statistics were based primarily upon the 1965 Health Interview Survey and the 1960-62 National Health Examination Survey, which had been published in a convenient form in 1969 as the Diabetes Source Book. Since the mechanism for revision and republication of these data was no longer available, the Workgroup decided to revise the most useful information, using more recent data when possible and incorporating the information from the (as yet unpublished) 1973 Health Interview Survey, more recent mortality statistics, and other data presently available.

The task of updating frequency data served to highlight the present deficiencies in the collection of data about diabetes and the lack of progress in this area over the past decade. It was apparent that there was an urgent need for compiling where possible, similar information lying outside the immediate charge of the Workgroup (for example, mortality statistics),so that an adequate perspective of the overall magnitude of the impact of diabetes could be obtained.

Deficiencies in the design and execution of present data collection, due to the failure to address appropriate questions, became obvious and will necessitate careful review of the mechanism(s) available to maintain the type, extent, and timeliness of statistical information necessary for public health decisions pertaining to diabetes.

The need for standardized definitions of diabetes and validation, when possible, of the reliability of morbidity and mortality data present additional challenges, which may help to explain and reduce some apparent inconsistencies within the available data. This need was further emphasized by the widely varying estimates of the frequency of diabetes in the nation given by both expert and lay witnesses alike in public testimony.

While we have presented data similar to that which would be contained in an updated Diabetes Source Book, we are fully aware of many deficiencies which are potentially remediable. We would, therefore, point out that there is a need for more complete data than we have been able to assemble at this time and recommend that, in the future, mechanisms should be instituted to review, improve, and make available at suitable intervals (perhaps every five years) an updated and more complete compilation of data on diabetes. Despite these caveats (which often exist in health statistics), reasonable and supportable data do exist to provide definition of many aspects of the scope of the disease and its economic and social impact on our society, and these data are presented.

However, the lack of improvement in quality, timeliness, and the broad base of health related statistics on diabetes from 1969 to the present does require that the Commission not accept the "status quo." It must instead explicitly recognize the opportunities to improve the data collection efforts; to expand the base of epidemiological research as a means to confirm incidence, prevalence, and sequelae; and to identify possible etiologic factors and research avenues. The recommendations and project summaries which follow contain our suggestions to the Commission for their consideration and action.

B.   DIABETES TABLES*

1.   INTRODUCTION

Diabetes is a chronic disease resulting from a relative or complete lack of insulin, the hormone produced in the pancreas necessary to the metabolism of carbohydrates. Where onset occurs in childhood or adolescence, there is usually a substantial lack of insulin secretion. Onset is precipitous, with most patients subsequently required to take insulin by injection on a continuing basis. Where onset occurs in adult life, it is usually gradual, often with only a partial loss of insulin secretion so that the patient can be maintained solely by diet restrictions. The disease is characterized by excessive thirst, hunger, and urination.

Diabetics are found in all parts of the world, among virtually all ethnic and racial groups. Rare, isolated exceptions have occasionally been reported in the literature (i.e., Eskimos). While accurate statistics are not available, some evidence indicates that morbidity and mortality are increasing in a number of countries. In the United States, available statistics on incidence, prevalence, and mortality

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*Prepared by Kurt Gorwitz, Sc.D., and Nancy Dixon, M.A.

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mong diabetics would indicate an annual increase in the last decade of
bout 6% in the number of recognized cases. Should this continue, the
umber of people with diabetes would double every 15 years. Although
here is some speculation as to the reasons for this apparent rise,
hese are in fact not known. For example, the possible impact of
reater awareness and accuracy in reporting cannot readily be determined.

In the United States, the number of reported diabetics is estimated
o be currently in excess of four million, or about 2% of the total pop-
lation. The annual number of new cases is 600,000, and the number of
eaths directly ascribed to diabetes is reported to be 38,000, making
t the fifth leading cause of mortality. In addition, it is a contribu-
ory factor annually in an estimated 80,000-100,000 deaths.

The U. S. Public Health Service has published several editions of
ts Diabetes Source Book in an effort to present the available facts
rom a variety of sources. Many of its tables updated and revised here
ocus on the incidence, prevalence, and etiology of diabetes. This
eport of the Committee on Scope and Impact contains useful compilations
f mortality from diabetes, life expectancy of diabetics, utilization of
edical services by diabetics, activity limitations of diabetics, occur-
ence of blindness due to diabetic retinopathy, complications in
regnancy among diabetic women, and economic impact.

DEFINITIONS

INCIDENCE: number of cases of a specified illness or condition
               newly diagnosed or reported during one year.

PREVALENCE: total number of cases of a specified illness or condi-
               tion diagnosed or reported as of a specified time
               period.

RATE: ratio of number of cases to population at risk.

AGE-SPECIFIC: number of cases in a specified age group
               as a ratio to the population at risk in
               the same age group.

AGE-ADJUSTED: a statistical procedure for removing the
               impact of different age distributions in
               two or more populations.

ETIOLOGY: causes or factors related to the occurrence of a
               disease.

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3.   INCIDENCE AND PREVALENCE TABLES

The incidence and prevalence of diabetes in the United States are not known. Estimates are available, however, based on information collected by the National Center for Health Statistics through its Health Interview Survey. Since these are derived from information from respondents, with no medical verification, they are subject to an undetermined error rate. Presumably, since the presence of diabetes in some adult household members may not be recognized, the number of false negatives would exceed the number of false positives. That is, there are probably more diabetics than indicated. The statistics in Tables 1 through 5 should, therefore, be clearly recognized as approximations whose principal value is that they provide some indication of the magnitude of the conditions and of differences between various cohorts.

The 1973 Health Interview Survey collected data from 40,000 households with 120,000 members. Of these, approximately 2,400 were reported to have diabetes. The sample size in some cells is, therefore, quite small and may be subject to considerable error. Rates by age-race and age-sex should, therefore, be interpreted with caution. Based on the information supplied, the number of known diabetics is estimated to be 4,191,000 (in 1973), or 2% of the total population (Table 1). This is 50% greater than the 2,772,000 reported in the 1969 edition of the Diabetes Source Book, based on 1965-66 Health Interview Survey statistics. Rates rose 40.7%, 26.4% for males (from 12.9 to 16.3) and 62.4% for females (from 16.1 to 24.1). In part, this difference may be due to the relatively much greater increase in the number of older females. Comparisons by specific age are not possible, since different age groupings were employed in the two periods. However, increases in early, middle, and old age appear to cluster around 50%. This increase is in line with projections derived from adding the estimated number of new cases and subtracting the estimated number of deaths among diabetics.

Rates in 1973 are consistently higher for females than for males, for nonwhites than for whites, and increase with advancing age. The highest rate, in excess of 10%, was noted for nonwhites 65 years of age or older. An estimated 86,000 diabetics (a rate of 1.3 per 1000) were under 17 years of age, a figure strikingly similar to the number derived from responses to a mail survey of Michigan's school districts. conducted by the author in 1972-73. The latter survey, limited to the ages five to 18, reported a rate of 1.6. Among chronic conditions, it is the second most frequently noted (Table 2).

The Health Interview Survey asked respondents reporting diabetes to indicate the date of onset of their condition. Based on the information supplied, the annual incidence is estimated to be 612,000, or 0.3% of the total population (Table 3). Of these, 35% are male, and 65% are female. Rates generally increase with advancing age, to a maximum

REPORTED PREVALENCE OF DIABETES (WITH RATE PER 1000) BY AGE SEX AND RACE

UNITED STATES 1973

	TOTAL		-17		17-44		45-64		65+	
SEX	#	RATE	#	RATE	#	RATE	#	RATE	#	RATE
TOTAL	4,191,000	20.4	86,000	1.3	704,000	8.9	1,813,000	42.5	1,589,000	78.5
M	1,620,000	16.3	35,000	1.1	261,000	6.9	819,000	40.6	506,000	60.3
F	2,571,000	24.1	51,000	1.6	443,000/10.8		995,000	44.4	1,083,000	91.3
RACE										
WHITE	3,570,000	19.9	74,000	1.4	576,000	8.3	1,518,000	39.6	1,402,000	75.9
OTHER	622,000	23.9	12,000	1.2	128,000/12.8		294,000	70.0	187,000	104.5

Source: Unpublished Health Interview Survey data, National Center for Health Statistics.

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TABLE 2

ESTIMATED MAJOR PREVALENCE FOR MAJOR CHRONIC CONDITIONS WITH RATES PER 1,000 POPULATION

Chronic Conditions	Estimated Prevalence	Estimated Rate	Causing Limitation of Activity	With One or More Physician Visits Past Year	Restricted Activity days per Condition per Year	Bed Days per Condition per Year
Migraine	4,480,000	21.8	3.2	47.9	8.7	4.1
Diabetes	4,191,000	20.4	29.7	82.6	14.6	5.8
Diseases of the Urinary System, NEC	2,725,000	13.2	5.8	76.2	8.3	3.5
Anemia, Unspecified	2,100,000	10.2	6.6	71.5	9.0	4.6
Other Specified Diseases of Thyroid Gland	1,702,000	8.3	6.0	72.3	3.8	1.2
Neuralgia, Neuritis, NOS, NEC	1,697,000	8.2	5.4	44.2	11.5	2.3
Disease of Uterus and Ovaries, NEC	1,394,000	6.8	9.3	84.9	17.3	8.2
Other Diseases of Kidney and Ureter, NEC	1,346,000	6.5	10.2	81.9	18.4	9.3
Other Specified Female Genital Disorders	1,301,000	6.3	8.7	56.7	19.1	7.1
Disease of Prostate	1,297,000	6.3	8.3	74.1	14.3	5.4

Source: Unpublished Health interview Survey

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REPORTED ANNUAL INCIDENCE OF DIABETES (WITH RATE PER 1,000) BY AGE AND SEX
UNITED STATES 1973

SEX	TOTAL		-17		17-44		45-64		65+	
	#	RATE	#	RATE	#	RATE	#	RATE	#	RATE
TOTAL	612,000	3.0	20,000	0.3	70,000	2.1	246,000	5.6	176,000	6.7
M	215,000	2.2	8,000	0.3	57,000	1.5	109,000	5.4	41,000	4.9
F	396,000	3.7	12,000	0.4	113,000	2.8	137,000	6.1	134,000	11.3

Source: Unpublished Health Interview Survey Data - National Center for Health Statistics.

annual incidence of 1.1% for females 65 years or older. The number of new cases under 17 years of age is estimated to be 20,000, 0.03% of the population in this age group.

Since accurate data are not available, incidence and prevalence estimates for individual states were derived by applying the national age-specific rates to the populations of the various states (Tables 4 and 5). Because they do not take into consideration variations due to racial, ethnic, or cultural differences, these figures are at best gross approximations. In the United States, 11% of the population is nonwhite. Since the diabetes rate of this population is estimated to be 20% higher than that of the white population, the figures shown should be increased or decreased by 0.2% for every percent of a state's nonwhite population above or below 11%. The estimated cumulative probability of contracting diabetes (Table 6) was estimated on the basis of reported age-sex incident rates. Females surviving to age 85 have a 35.4% probability of diabetes compared with 23.2% for males. Table 7 shows incidence and prevalence by family income.

4. POSTSCRIPT

Meaningful data collection and analysis should be directed toward providing answers to specific questions with formulated purposes.

For example, one purpose underlying the collection of prevalence data for diabetes could be determination of the importance in the United States of diabetes relative to other chronic conditions as defined by the number of people known to be affected by the disease. For that express purpose, the data presented in Table 1 were appropriately collected. However, an affirmative answer to the question "Do you have diabetes?" does not in itself adequately fulfill the purpose of ascertaining the importance of diabetes, in this country, which can be only partially grasped by determining the relative number of persons affected. In addition to establishing the relative frequency of diabetes, a further need is to compare its impact on the affected individuals.

Persons with insulin-dependent diabetes and those with insulin-independent diabetes have different natural histories. Yet, in part because the purposes of questions related to each type of diabetes have not been formulated with health statisticians, national data which differentiate between these types of diabetes are not available.

Defining the purpose and uses of statistics on diabetes is too time consuming to be accomplished within the time available to the ad hoc Workgroup who compiled this report. Therefore, this should be recognized as an initial, limited effort.

A permanent task force charged with the periodic production of a diabetes source book needs to be established. It would have to give

TABLE 4

ESTIMATED PREVALENCE OF DIABETES BY AGE, REGION, AND STATE *
1974

	TOTAL	-18	18-44	45-64	65+
TOTAL	4,348,600	87,400	703,100	1,845,500	1,712,600
NORTHEAST	1,075,000	19,500	159,800	468,600	427,000
MAINE	22,400	400	3,300	9,100	9,600
NEW HAMPSHIRE	16,600	300	2,700	6,800	6,800
VERMONT	9,500	200	1,600	3,700	4,000
MASSACHUSETTS	125,600	2,300	19,100	52,300	51,900
RHODE ISLAND	21,000	400	3,000	8,900	8,700
CONNECTICUT	65,100	1,200	10,200	29,100	24,600
NEW YORK	393,600	7,100	59,300	170,400	156,800
NEW JERSEY	156,400	3,000	23,500	71,200	58,800
PENNSYLVANIA	264,800	4,600	37,200	117,100	105,800
NORTH CENTRAL	1,179,900	24,300	189,300	493,800	472,600
OHIO	216,500	4,500	35,600	94,000	82,400
INDIANA	105,900	2,300	17,800	44,900	41,000
ILLINOIS	229,100	4,600	36,600	98,800	89,000
MICHIGAN	173,600	4,000	30,600	76,300	62,600
WISCONSIN	94,800	1,900	14,800	38,400	39,600
MINNESOTA	79,900	1,700	12,900	31,400	33,900
IOWA	63,200	1,200	8,900	24,800	28,300
MISSOURI	105,200	1,900	15,400	41,500	46,400
NORTH DAKOTA	13,300	300	2,000	5,400	5,700
SOUTH DAKOTA	14,900	300	2,100	5,900	6,600
NEBRASKA	33,500	600	5,000	12,900	15,000
KANSAS	50,000	900	7,500	19,600	22,100

* Computed by the authors on the basis of national age-specific prevalence rates.

PREVALENCE

	TOTAL	-18	18-44	45-64	65+
SOUTH	1,360,600	28,300	224,700	566,500	541,100
DELAWARE	10,900	200	2,000	4,900	3,800
MARYLAND	77,600	1,700	14,300	35,400	26,100
WASHINGTON, D. C.	14,600	300	2,700	6,100	5,600
VIRGINIA	93,300	2,000	17,500	41,600	32,200
WEST VIRGINIA	39,600	700	5,600	17,100	16,200
NORTH CAROLINA	103,400	2,200	18,700	45,300	37,100
SOUTH CAROLINA	50,400	1,200	9,700	22,200	17,200
GEORGIA	90,300	2,100	17,000	38,800	32,400
FLORIDA	201,700	3,000	24,400	74,800	99,500
KENTUCKY	69,300	1,400	11,000	28,300	28,600
TENNESSEE	84,900	1,700	13,900	35,600	33,700
ALABAMA	72,100	1,500	11,700	30,200	28,700
MISSISSIPPI	45,800	1,100	7,300	18,100	19,300
ARKANSAS	45,900	900	6,400	17,900	20,700
LOUISIANA	70,300	1,700	12,400	29,700	26,500
OKLAHOMA	59,300	1,100	8,900	23,600	25,700
TEXAS	231,300	5,200	41,100	97,000	87,900
WEST	733,100	15,400	129,300	316,600	271,800
MONTANA	14,800	300	2,400	6,400	5,700
IDAHO	15,600	400	2,600	6,700	6,000
WYOMING	7,000	200	1,200	3,200	2,500
COLORADO	45,800	1,100	9,100	19,600	16,000
NEW MEXICO	19,700	500	3,800	8,600	6,800
ARIZONA	42,300	1,000	7,100	17,700	16,600
UTAH	19,700	600	4,000	8,200	6,900
NEVADA	10,600	200	2,000	5,200	3,200
WASHINGTON	70,700	1,400	11,900	29,500	27,800
OREGON	48,400	900	7,500	20,300	19,700
CALIFORNIA	419,800	8,300	73,300	182,300	155,900
ALABAMA	4,200	200	1,400	2,000	600
HAWAII	14,500	400	3,100	6,900	4,200

TABLE 5

ESTIMATED INCIDENCE OF DIABETES BY AGE, REGION, AND STATE *
1974

	TOTAL	-18	18-44	45-64	65+
TOTAL	629,800	21,400	169,500	250,500	188,500
NORTHEAST	154,100	4,800	38,500	63,600	47,200
MAINE	3,200	100	800	1,200	1,100
NEW HAMPSHIRE	2,400	100	600	900	700
VERMONT	1,300	100	300	500	400
MASSACHUSETTS	18,000	600	4,600	7,100	5,700
RHODE ISLAND	3,000	100	700	1,200	1,000
CONNECTICUT	9,400	300	2,500	3,900	2,700
NEW YORK	56,500	1,700	14,300	23,100	17,300
NEW JERSEY	22,500	700	5,700	9,700	6,500
PENNSYLVANIA	37,700	1,100	9,000	15,900	11,700
NORTH CENTRAL	170,900	6,000	45,600	67,000	52,300
OHIO	31,600	1,100	8,600	12,800	9,100
INDIANA	15,500	600	4,300	6,100	4,500
ILLINOIS	33,200	1,100	8,800	13,400	9,800
MICHIGAN	25,600	1,000	7,400	10,400	6,900
WISCONSIN	13,600	500	3,600	5,200	4,400
MINNESOTA	11,500	400	3,100	4,300	3,800
IOWA	8,900	300	2,200	3,400	3,100
MISSOURI	15,000	500	3,700	5,600	5,100
NORTH DAKOTA	1,900	100	500	700	600
SOUTH DAKOTA	2,100	100	500	800	700
NEBRASKA	4,800	200	1,200	1,800	1,700
KANSAS	7,100	200	1,800	2,700	2,400

*Computed by the authors on the basis of national age-specific incidence rates.

	TOTAL	-18	18-44	45-64	65+
SOUTH	196,900	6,900	54,200	76,900	58,90
DELAWARE	1,600	100	500	700	40
MARYLAND	11,600	400	3,500	4,800	2,90
WASHINGTON, D. C.	2,200	100	700	800	60
VIRGINIA	13,900	500	4,200	5,600	3,60
WEST VIRGINIA	5,600	200	1,300	2,300	1,80
NORTH CAROLINA	15,300	500	4,500	6,100	4,10
SOUTH CAROLINA	7,600	300	2,300	3,000	1,90
GEORGIA	13,500	500	4,100	5,300	3,60
FLORIDA	27,800	700	5,900	10,100	11,00
KENTUCKY	10,000	300	2,700	3,800	3,20
TENNESSEE	12,300	400	3,400	4,800	3,70
ALABAMA	10,500	400	2,800	4,100	3,20
MISSISSIPPI	6,600	300	1,800	2,500	2,10
ARKANSAS	6,500	200	1,500	2,400	2,30
LOUISIANA	10,400	400	3,000	4,000	2,90
OKLAHOMA	7,500	300	2,100	3,200	1,90
TEXAS	34,100	1,300	9,900	13,200	9,70
WEST	108,000	3,700	31,200	43,000	30,10
MONTANA	2,200	100	600	900	6
IDAHO	2,300	100	600	900	7
WYOMING	1,000	*	300	400	3
COLORADO	6,900	300	2,200	2,700	1,80
NEW MEXICO	3,000	100	900	1,200	7
ARIZONA	6,200	200	1,700	2,400	1,80
UTAH	3,000	100	1,000	1,100	80
NEVADA	1,600	100	500	700	40
WASHINGTON	10,300	300	2,900	4,000	3,10
OREGON	7,000	200	1,800	2,800	2,20
CALIFORNIA	61,700	2,000	17,700	24,700	17,20
ALABAMA	700	*	300	300	10
HAWAII	2,200	100	800	900	50

*Less than fifty

TABLE 6

ESTIMATED CUMULATIVE PROBABILITY (PERCENT) OF CONTRACTING
DIABETES BY SEX AND ATTAINED AGE*

Attained Age (In Years)	Total	Male	Female
17	0.6	0.5	0.8
45	6.3	5.6	8.3
65	16.7	15.3	18.8
85	26.0	23.2	35.4

*Estimated on the basis of currently available incidence data.

TABLE 7

INCIDENCE AND PREVALENCE RATES (PER 1,000) OF DIABETES
BY REPORTED FAMILY INCOME
UNITES STATES
1973

REPORTED FAMILY INCOME	INCIDENCE (NEW CASES IN PRECEDING YEAR)	PREVALENCE (TOTAL CASES)
TOTAL	3.0	20.4
Less Than $5,000	4.5	40.2
$5,000 – $9,999	3.4	20.0
$10,000 or More	2.2	13.7

Source: Computed by the authors from unpublished Health Interview Survey Data, National Center for Health Statistics.

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high priority to the definition of purposes so as to specify the ques-
tions and judge the adequacy of data and analysis, and then recommend
changes and innovations for further data collection (Figures 1-7).

C.   ETIOLOGIC FACTORS

1.   OBESITY AND NUTRITIONAL FACTORS*

a.   Statement of the Problem

It is known that nutritional factors play a major role in deter-
mining the risk of diabetes. This may help explain why its incidence
varies as much as tenfold in different societies. However, lack of
adequate knowledge about nutritional factors and the risk of diabetes
cannot be stressed enough. It is not known, for example, whether con-
sumption of sugar increases risk of diabetes; it is not known what part,
if any, nutrition plays in determining risk of diabetes in juveniles.

It is known that obesity is the nutritional factor having the
strongest relationship to the risk of diabetes. That risk is increased
about twofold in mildly obese persons, about fivefold in moderately
obese persons, and more than tenfold in people who are very fat. Also,
present evidence suggests that prevention of hyperglycemia by preven-
tion of obesity would also mitigate substantially the risk of vascular
lesions that plague obese diabetics.

Strong emphasis should be placed on the potentialities for
developing more efficient and effective preventive methods through epi-
demiologic investigation and related basic and clinical research.

b.   Impact of the Problem

The discussion in Section C shows that risk of diabetes is
increased even in those who are only 10 to 20% overweight. This means
that approximately one-third of the middle-aged men and approximately
one-half of middle-aged women in the United States face an increased
risk of diabetes. If present trends continue, roughly 10% of the popu-
lation in the United States can expect to develop fasting hyperglycemia.
Moreover, recent evidence suggests that fat persons with mild impair-
ment of glucose tolerance are diabetic in the sense that they are more
likely to develop certain vascular lesions. In the general population
of Tecumseh, Michigan, for example, this increased risk of vascular
lesions extended as far down as the 20th percentile when their blood
glucose values were ranked. Evidence to be described below suggests

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*Prepared by Dr. K. West and Dr. E. Bierman.

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FIGURE 1

INCIDENCE AND PREVALENCE RATES (PER 1000) OF DIABETES BY REPORTED FAMILY INCOME UNITED STATES 1973
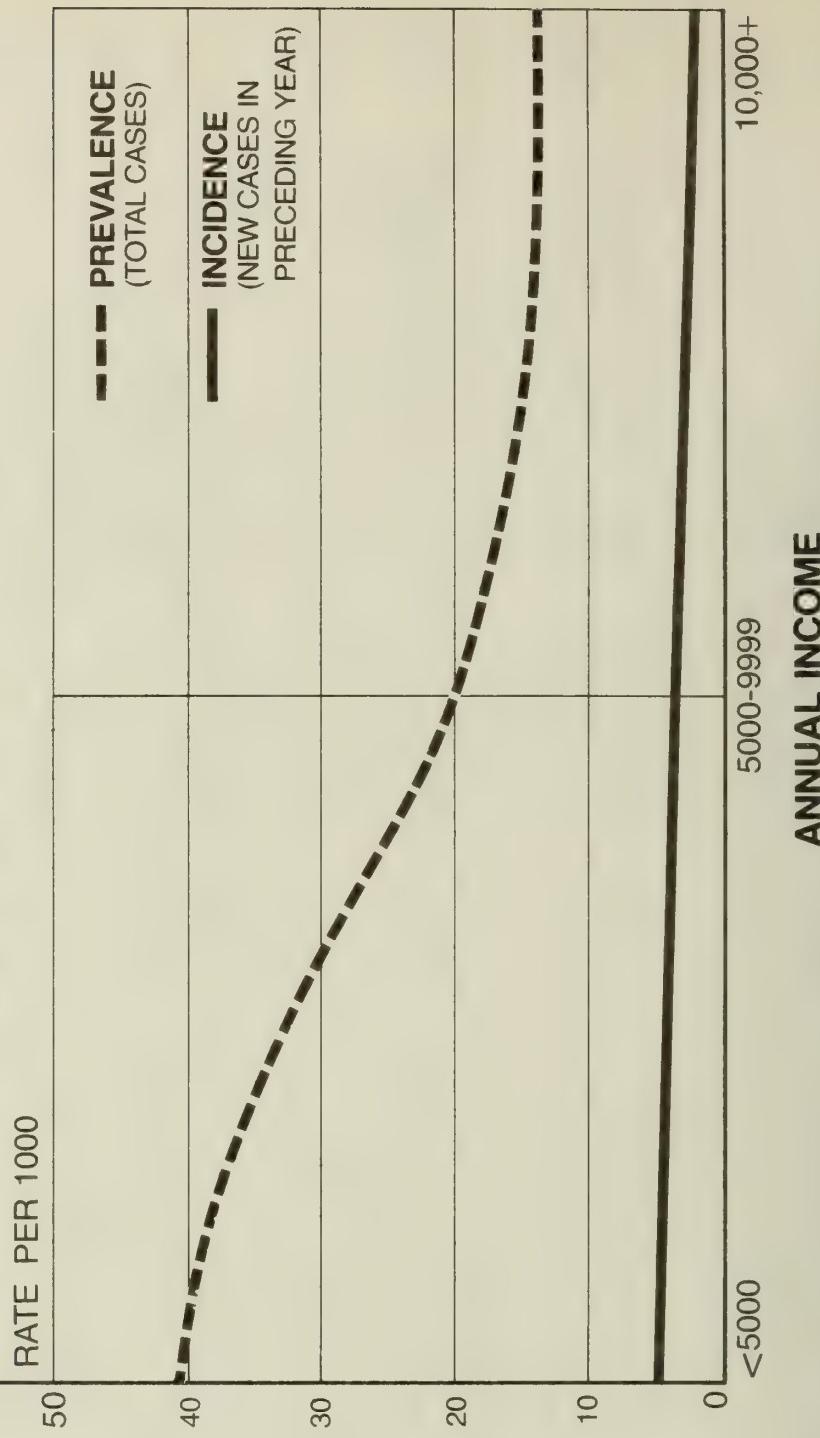
SOURCE: UNPUBLISHED HEALTH INTERVIEW SURVEY DATA, NATIONAL CENTER FOR HEALTH STATISTICS.

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FIGURE 2

REPORTED DIABETES PREVALENCE
RATE BY AGE AND SEX, 1973

RATE PER 1000

FEMALE
MALE

100

80

60

40

20

0

UNDER 17   17-44   45-64   65+

AGE (IN YEARS)
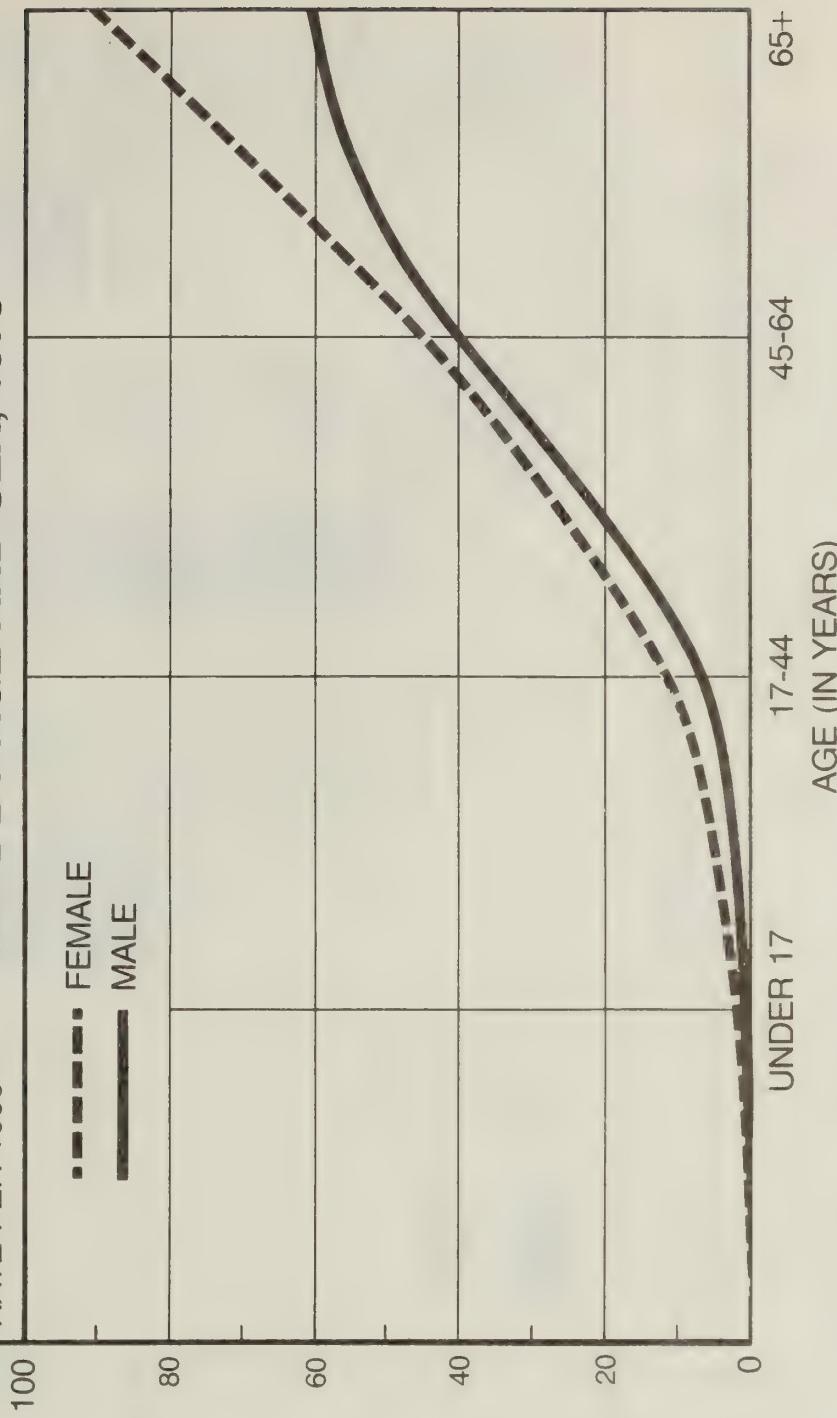
SOURCE: HEALTH INTERVIEW SURVEY – 1973. NATIONAL CENTER FOR HEALTH STATISTICS

FIGURE 3

REPORTED DIABETES INCIDENCE
RATE BY AGE AND SEX, 1973
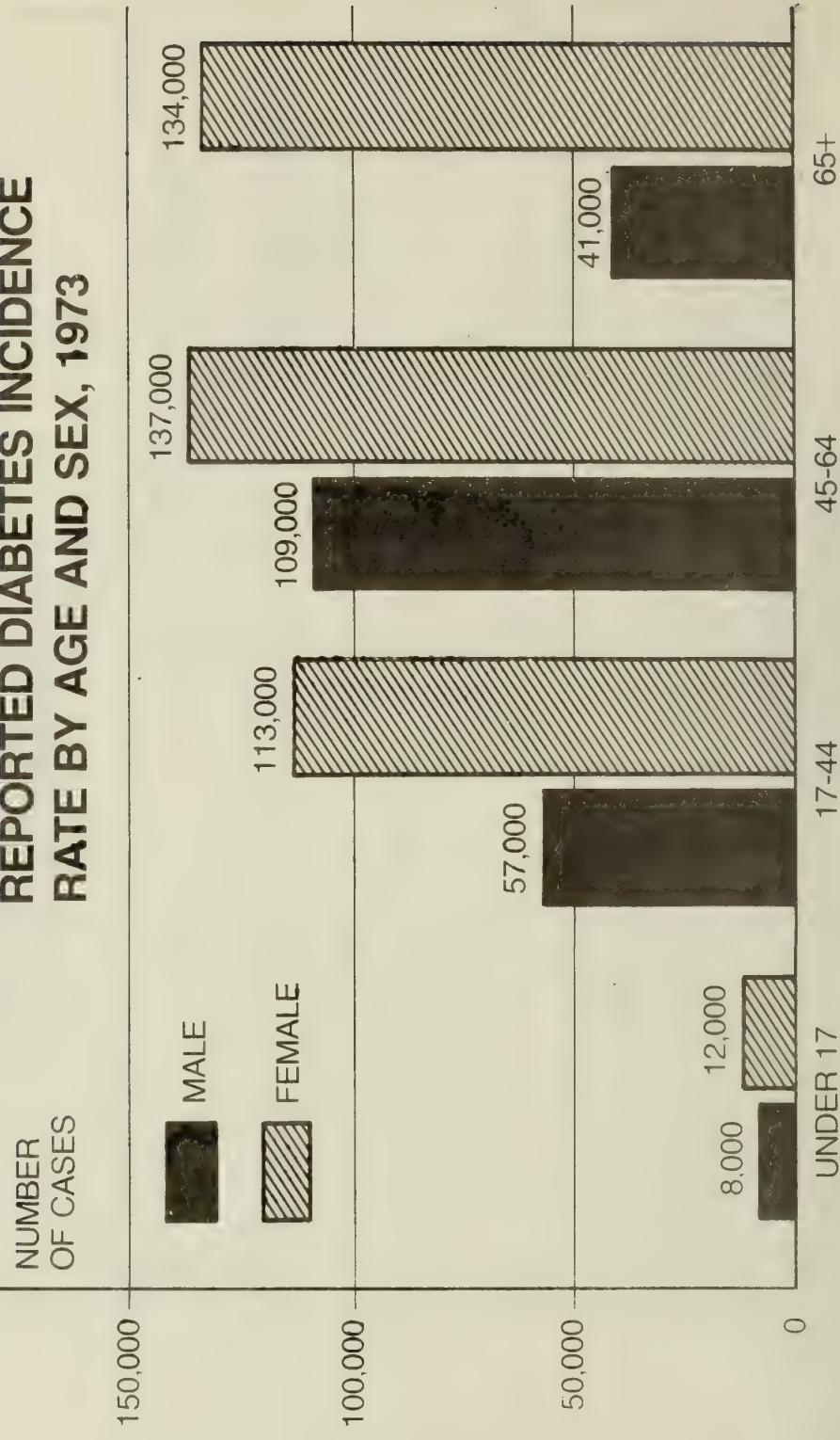
NUMBER
OF CASES

MALE

FEMALE

150,000

100,000

50,000

0

UNDER 17   17-44   45-64   65+

8,000   12,000   57,000   113,000   109,000 137,000   41,000   134,000

SOURCE: HEALTH INTERVIEW SURVEY – 1973. NATIONAL CENTER FOR HEALTH STATISTICS

FIGURE 4

REPORTED DIABETES PREVALENCE RATE BY AGE AND RACE, 1973

RATE PER 1000

- - - NONWHITE
—— WHITE

AGE (IN YEARS)

UNDER 17   17-44   45-64   65+

SOURCE HEALTH INTERVIEW SURVEY – 1973. NATIONAL CENTER FOR HEALTH STATISTICS

FIGURE 5

REPORTED NUMBER OF DIABETICS
RATE BY AGE AND SEX, 1973

NUMBER
OF DIABETICS

MALE

FEMALE

SOURCE: HEALTH INTERVIEW SURVEY – 1973. NATIONAL CENTER FOR HEALTH STATISTICS
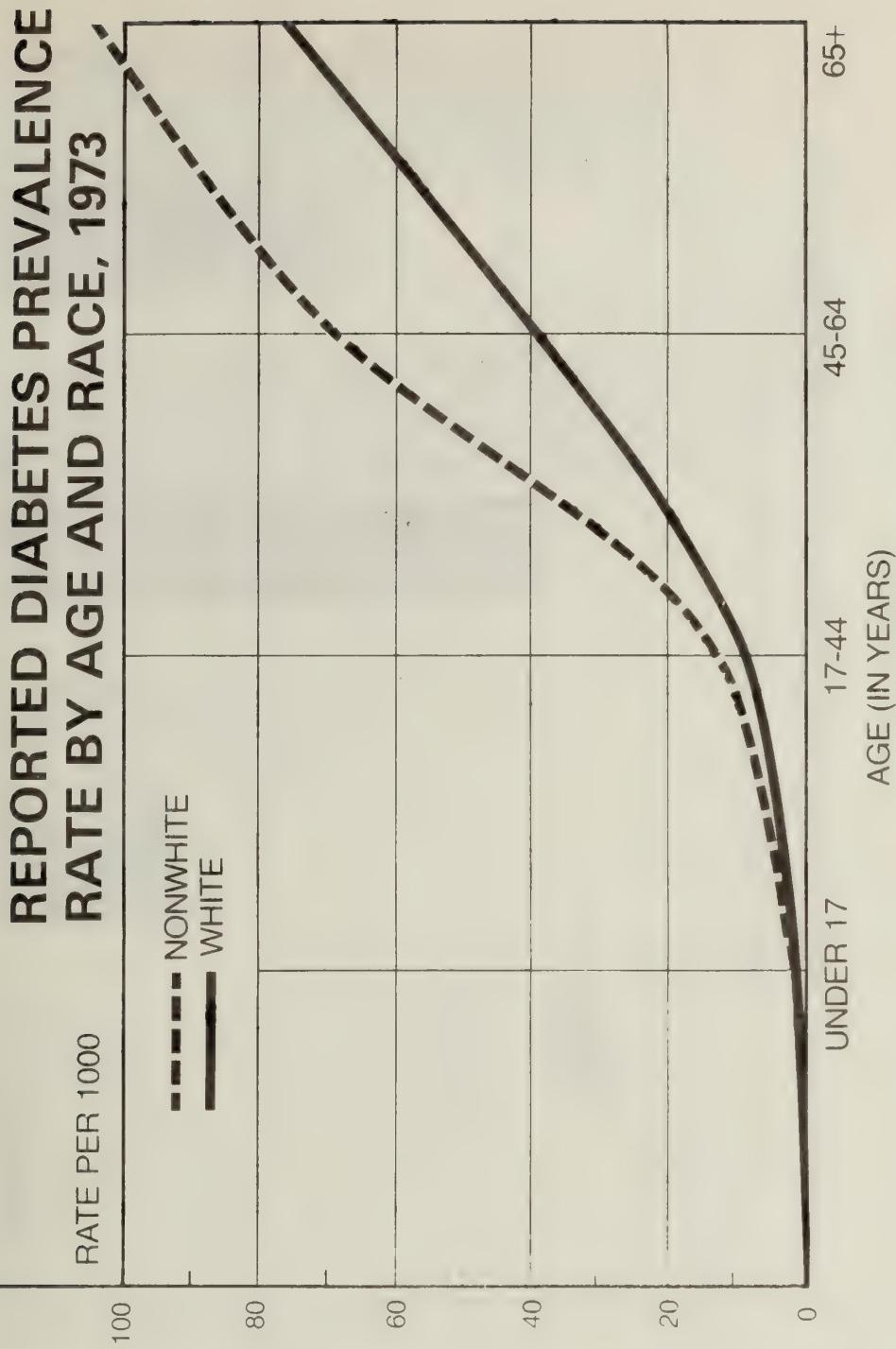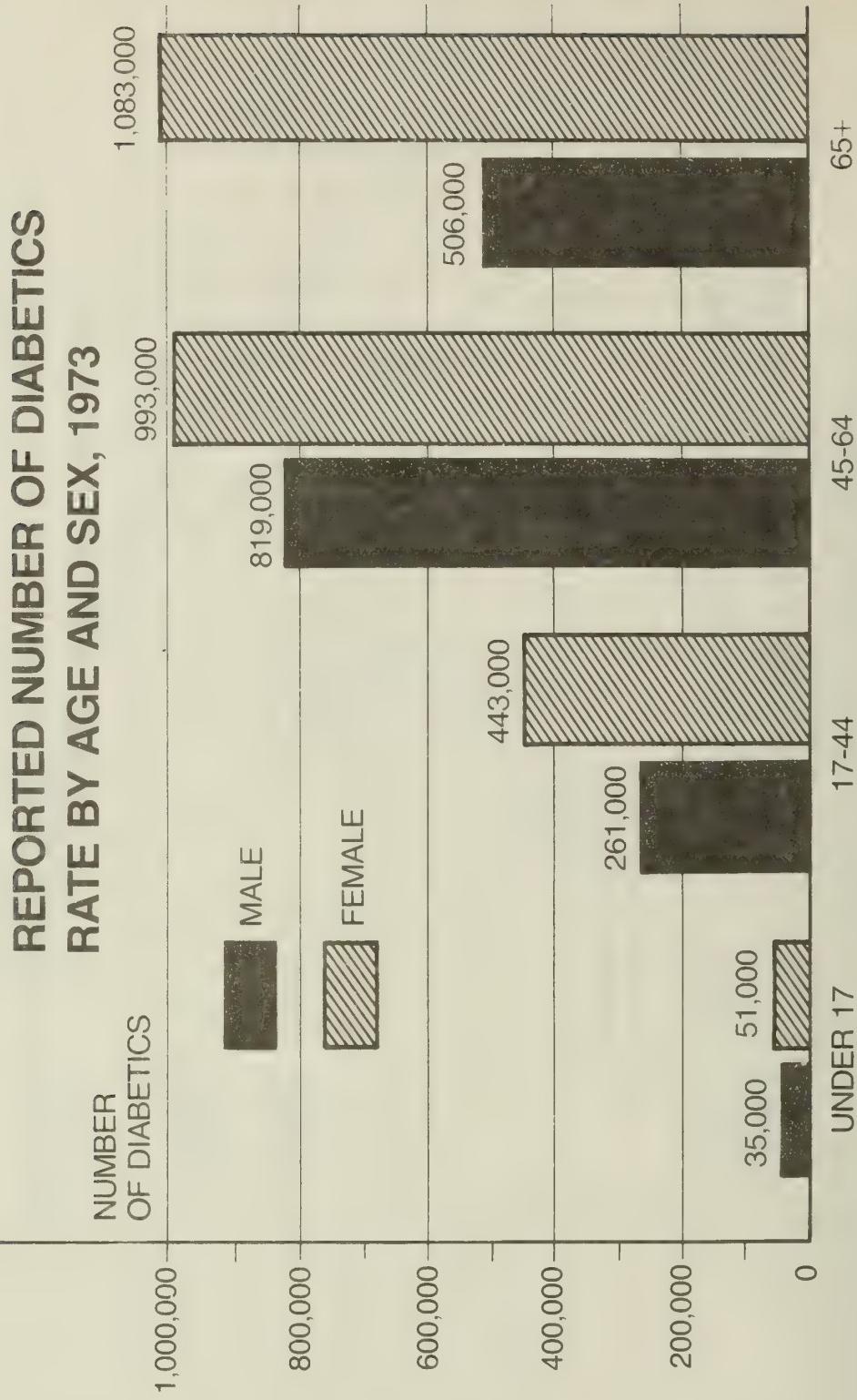
FIGURE 6

REPORTED DIABETES INCIDENCE
RATE BY AGE AND SEX, 1973
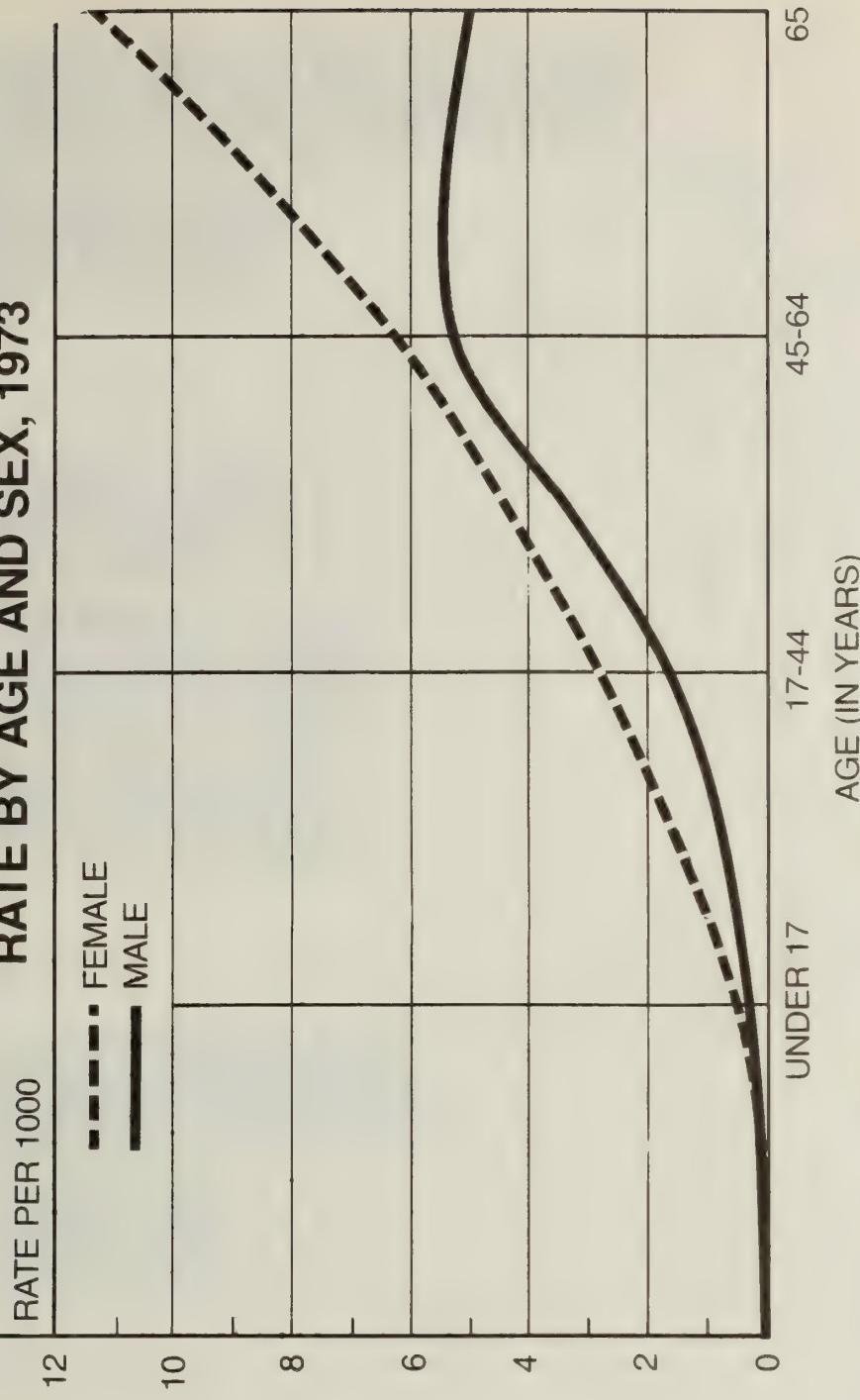
RATE PER 1000

- - - FEMALE
—— MALE

12
10
8
6
4
2
0

UNDER 17   17-44   45-64   65 +

AGE (IN YEARS)

SOURCE: HEALTH INTERVIEW SURVEY – 1973. NATIONAL CENTER FOR HEALTH STATISTICS

FIGURE 7

CHANGES IN REPORTED PREVALENCE
BY SEX, AGE AND RACE – 1965-66 & 1973

SOURCE HEALTH INTERVIEW SURVEY – 1973. NATIONAL CENTER FOR HEALTH STATISTICS
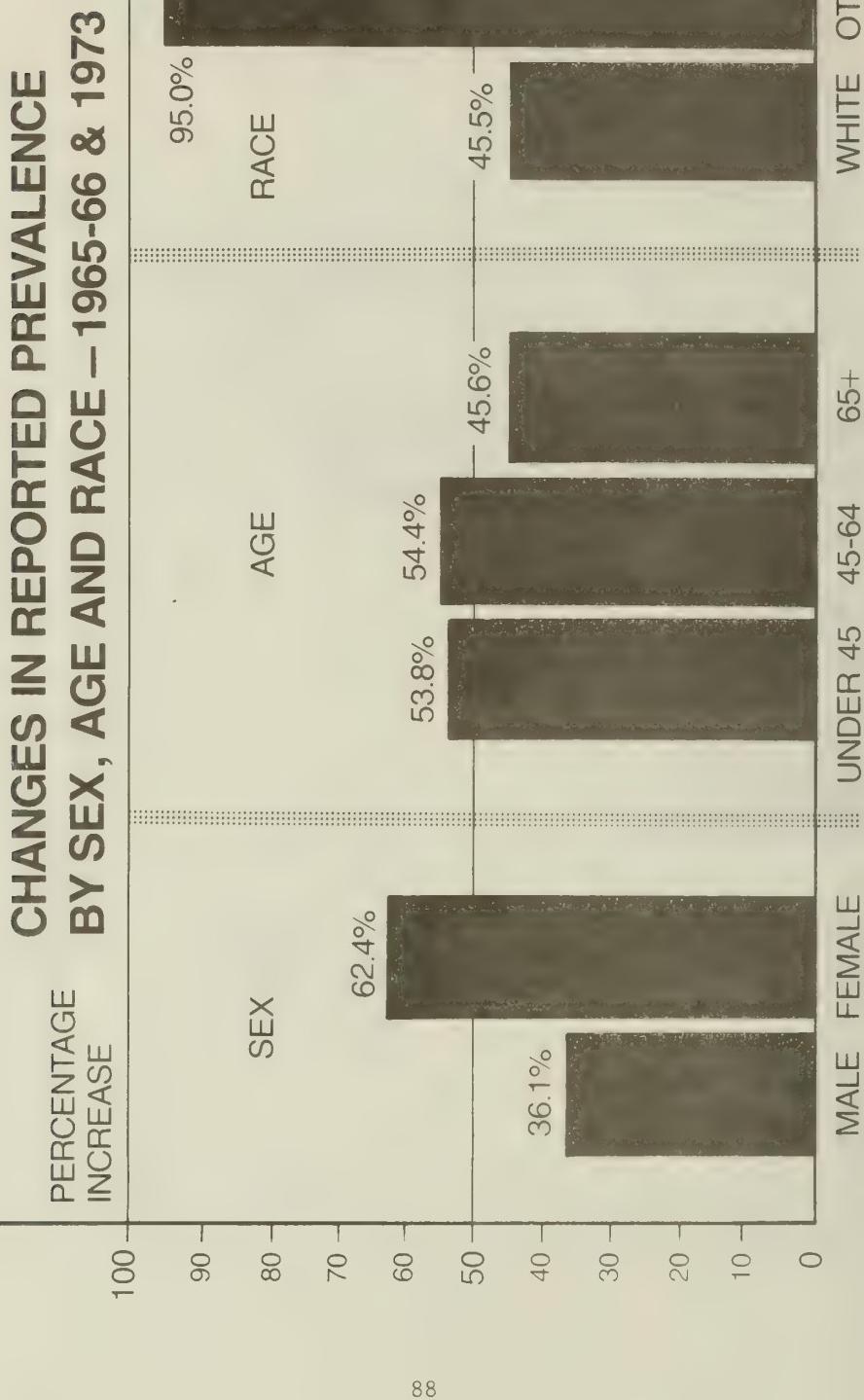
that obesity is responsible for a substantial majority of diabetes in the United States. This does not mean that genetic factors are unimportant, but it is clear that leanness protects to a marked degree, even among those who have a genetic predisposition to diabetes.

1) Frequency of Obesity in the United States and Its Effect on Risk of Diabetes:

During the years 1960-1962, the National Center for Health Statistics did an extensive study of the height, weight, and other measurements of adiposity on a representative sample of Americans of various ages. It shows that we have become too fat. In men from 45-54 years of age, average height was 5 feet 8 inches. Average nude weight in these men was 164 pounds. By traditional standards promulgated by the Metropolitan Life Insurance Company, the ideal weight of men of this height when measured in clothing extends from 136 to 170 pounds. Here it is assumed that a height of 5 feet 8 inches without shoes is equivalent in men to a height of 5 feet 9 inches with shoes. It has been estimated that the weight of the clothing (including shoes) of these men would average 8 pounds. Thus, ideal nude weight for this height ranges from 128 to 162 pounds. The mean of this range is 145 pounds. Thus, the average middle-aged man is 25 pounds overweight. His weight is beyond the range of the insurance company standard and 17% above the mean weight in this range. Some of the standards that have been employed in defining "obesity" have more generous limits, but by any standards, at least one-third of American middle-aged men are fat.

Womem are even fatter. The average height without shoes of the women in the national sample was 5 feet 3 inches. Average nude weight was 145 pounds. By Metropolitan Life Insurance Company standards, the ideal weight of women as ordinarily dressed, who are 5 feet 5 inches in heels (equivalent to 5 feet 3 inches without shoes) ranges from 111 pounds to 142 pounds to 142 pounds. Since weight of clothing and shoes averages 5 pounds in women, this correction suggests a standard ranging from 106 to 137 pounds with a mean of 121 pounds. Thus, the average middle-aged American woman who weighs 145 pounds is about 24 pounds overweight (approximately 20%). In this age group, median nude weight was 141 pounds, or 18% above the mean of the standard range. Thus, about 40 to 60% of American women in this age group are obese, depending on standards employed. Moreover, older women are even fatter. In women from 55 to 64 years of age, average nude weight was 150 pounds and mean nude weight was 144 pounds. In American men, weight declined somewhat after reaching age 54.

Other indices of fatness showed very similar results. This includes measurement of the thickness of subcutaneous fat, waist girth, etc. It is widely believed that Americans are becoming fatter. However, very little direct evidence is available. In women studied by the

Society of Actuaries in 1959, the average weight for a given height at age 25 was five to six pounds less than observed in a similar study performed between 1909-1927. Weight was two to four pounds greater for men in the more recent study after appropriate adjustments for height. It is, of course, possible that both men and women were more muscular in the early part of this century. The latter data are by no means conclusive because of a number of factors which include uncertainty about accuracy of recorded weights of persons who apply for insurance and the possibility that the characteristics of the universe of subjects who apply for insurance may change over time with respect to factors such as social and economic status and others.

Studies in whole communities, such as Tecumseh and Framingham, generally tend to confirm the data of the National Center for Health Statistics summarized above. Special populations that are very fat are of particular interest. These include certain, but not all, tribes of Indians. Some of these tribes are exceedingly fat and, in general, rates of diabetes closely parallel rates and degrees of adiposity (7). Published and unpublished data of the National Center for Health Statistics show that black women are fatter than white women and much fatter than black men. These increased rates and amounts of obesity are associated with very high rates of diabetes. Data are rather limited concerning this epidemic of obesity and diabetes in black women, but observations are sufficient to indicate that this phenomenon deserves more attention than it has received.

2) Obesity as a Cause of Diabetes:

A very few studies here and abroad, including those of Medley (1964) in England, and one by O'Sullivan (1965) in Oxford, Massachusetts, have shown little effect of obesity on risk of diabetes (29, 30). However, examination of the circumstances of these studies and of evidence developed in other studies suggests very strongly that obesity is regularly a very strong risk factor for diabetes. Also, Jackson (1968) reported one group of black women in South Africa who had low rates of diabetes despite fairly considerable weight in relation to height (31). One of several possibilities in the latter group is that duration of obesity had been brief.

We are unaware of any reports of lean populations or sub-populations in which rates of diabetes are high. Studies abroad confirming the strong relationship of obesity and risk of diabetes include the report of Pyorala and his associates (1974) in Helsinki policemen, in whom prevalence and incidence of diabetes were found to be increased by a factor of four in obese men from 30 to 59 years of age (32). Medalie (1975) has made similar observations in Israel (33). Several figures are attached. Figure 8 summarizes studies by Rimm (1975) in 73,352 women who were members of a weight-reducing club. In all age

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FIGURE 8

OBESITY AND AGE-SPECIFIC OCCURRENCE RATES
FOR WOMEN WITH A HISTORY OF ADULT
ONSET OF DIABETES

RATE
PER 100

50-59
YEARS

40-49
YEARS

30-39
YEARS

20-29
YEARS
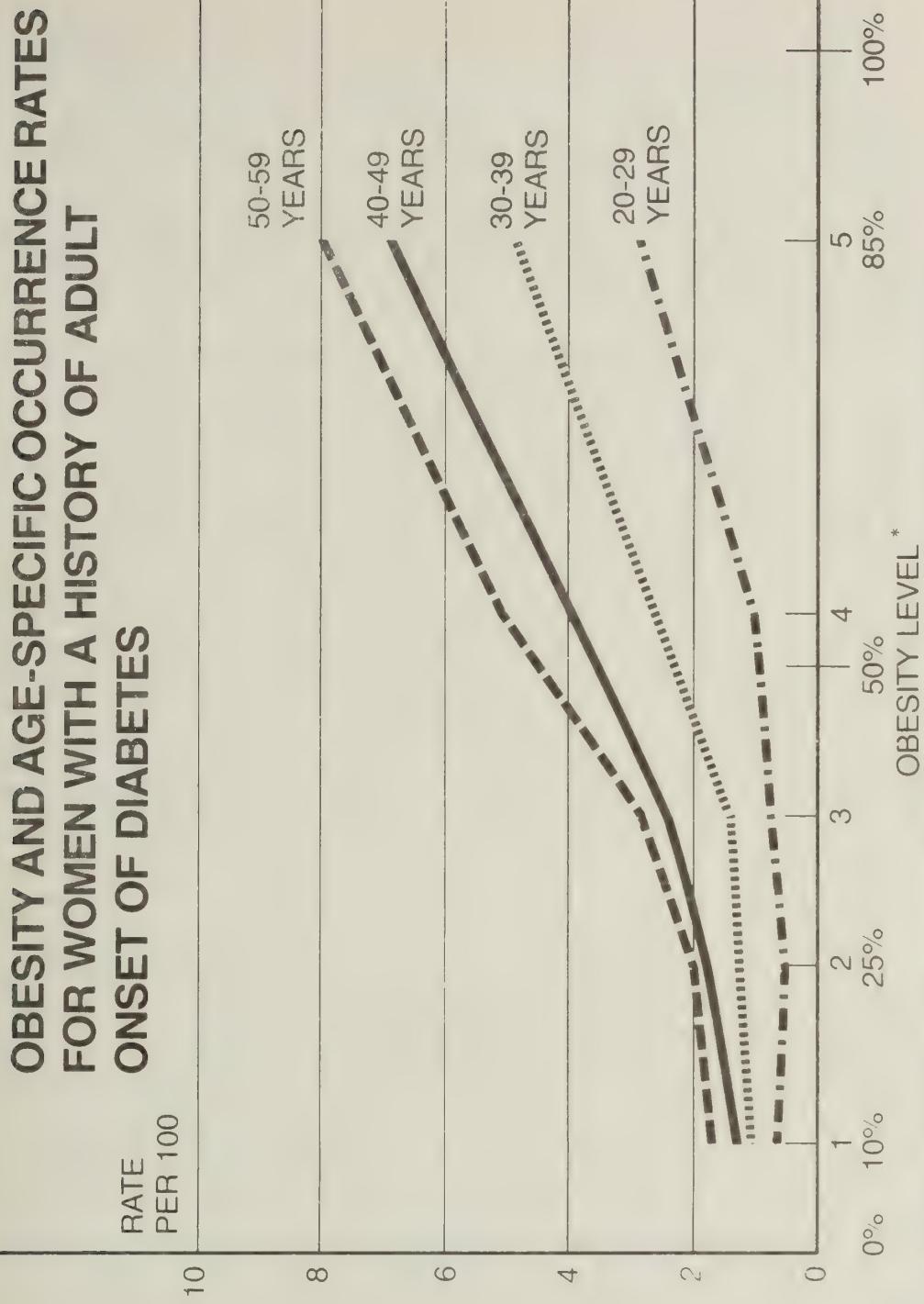
OBESITY LEVEL *

NOTE OBESITY LEVEL IS EXPRESSED ON A SCALE OF PERCENTAGE ABOVE IDEAL WEIGHT

SOURCE DATA OF A A RIMM et al – PUBLIC HEALTH REPORTS
90 p 48. 1975 – 73.352 WOMEN (MEMBERS OF "TOPS" CLUBS)

groups, prevalence of diabetes was closely associated with degree of fatness. Women in their third decade tolerated moderate and severe obesity with only modest increases in rates of diabetes. **Figure 9** presents data of Westlund (1972) showing a highly dramatic relationship between fatness and incidence of diabetes in 3,751 Oslo men who were followed for ten years after an initial examination in their fifth decade of life. Incidence rates in very fat men were more than 20 times greater than in the non-obese. It is also of considerable interest that incidence rates were exceedingly low in the lean subjects. **Figures 10** and 11 show the profound effect of obesity on diabetes in federal employees. Data in Pimas are similar (Hammah and Miller, 1975) (34).

3) Anatomic Distribution of Adiposity and Risk of Diabetes:

Friedman and his associates reported in 1969 that risk of diabetes seemed to be greater in subjects with central adiposity of the trunk as contrasted to equally fat persons who had more of their total body fat in the subcutaneous depots of their extremities (35). Vague and his associates (36, 37) had reported similar findings previously. West et al. (38) described the distribution of subcutaneous fat in a group of Kiowa and Comanche Indians in Oklahoma in whom rates of diabetes were exceedingly high. These individuals had a much greater percentage of their fat at the subscapular depot and a lesser portion at the triceps area when compared to the general population of the United States. In part, this peculiar distribution is attributable to the fact that in these Indians obesity usually comes on after maturity. Even in whites, those who become obese later in life tend to have a more central distribution of their adiposity. More information is needed concerning the causes and effects of these differences in distribution of body weight.

c. State of the Art

It has long been suspected that nutritional factors affect the risk of diabetes. More recent investigations elucidate further the nature and strength of these relationships. Changing dietary patterns in Japan (1), Israel (2), and Africa (3) have been associated with a profound increase in the rates of diabetes. Studies by West with Kalbfleisch and other collaborators in 13 societies of 11 countries indicate a strong relationship of diabetes prevalence and nutritional factors (4-6). A recent review of available data on past and present rates of diabetes in aboriginal populations of the New World (Indians, Eskimos, Polynesians, and Micronesians) also suggests a strong relationship of diet and a risk of diabetes (7). Marked differences in nutritional factors and exercise levels in these populations probably account for differences in rates of diabetes as great as tenfold (7).

FIGURE 9

AGE-ADJUSTED 10-YEAR INCIDENCE OF FIRST
DIAGNOSIS OF DIABETES MELLITUS RELATED
TO WEIGHT-HEIGHT RELATIONSHIP
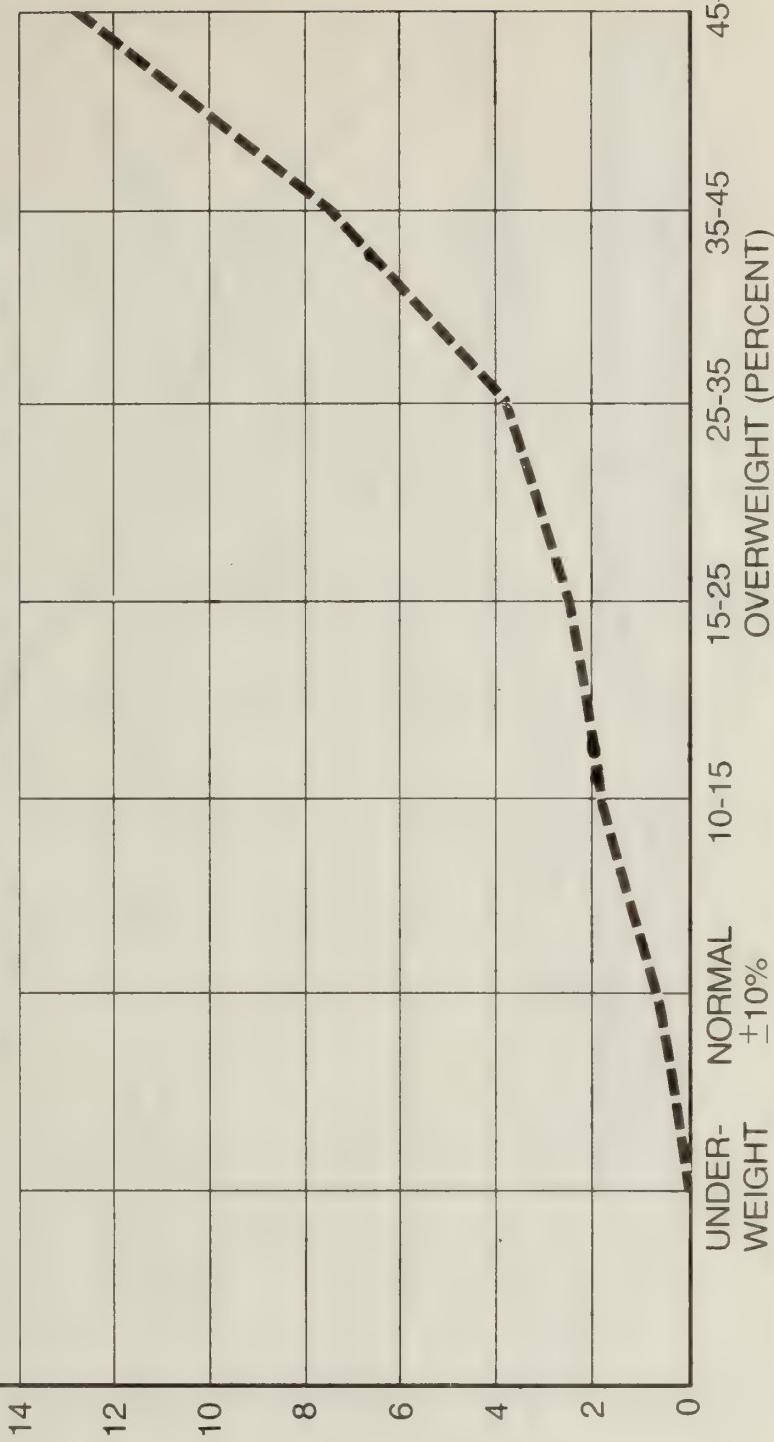
SOURCE: DATA OF WESTLUND – 3,751 MEN OF OSLO AGE 40-49 INITIALLY.
(SCAND. J. OF CLIN. AND LAB. INVEST., v. 30. Suppl. 127. p. 21)

FIGURE 10

FEDERAL EMPLOYEE DIABETES SCREENING: NEW
CASES PER 1,000 SCREENED, BY WEIGHT STATUS,
JULY 1963–JUNE 1964

DIABETES RATES RISE AS WEIGHT INCREASES

SOURCE: DIABETES AND ARTHRITIS CONTROL PROGRAM. PUBLIC HEALTH SERVICE

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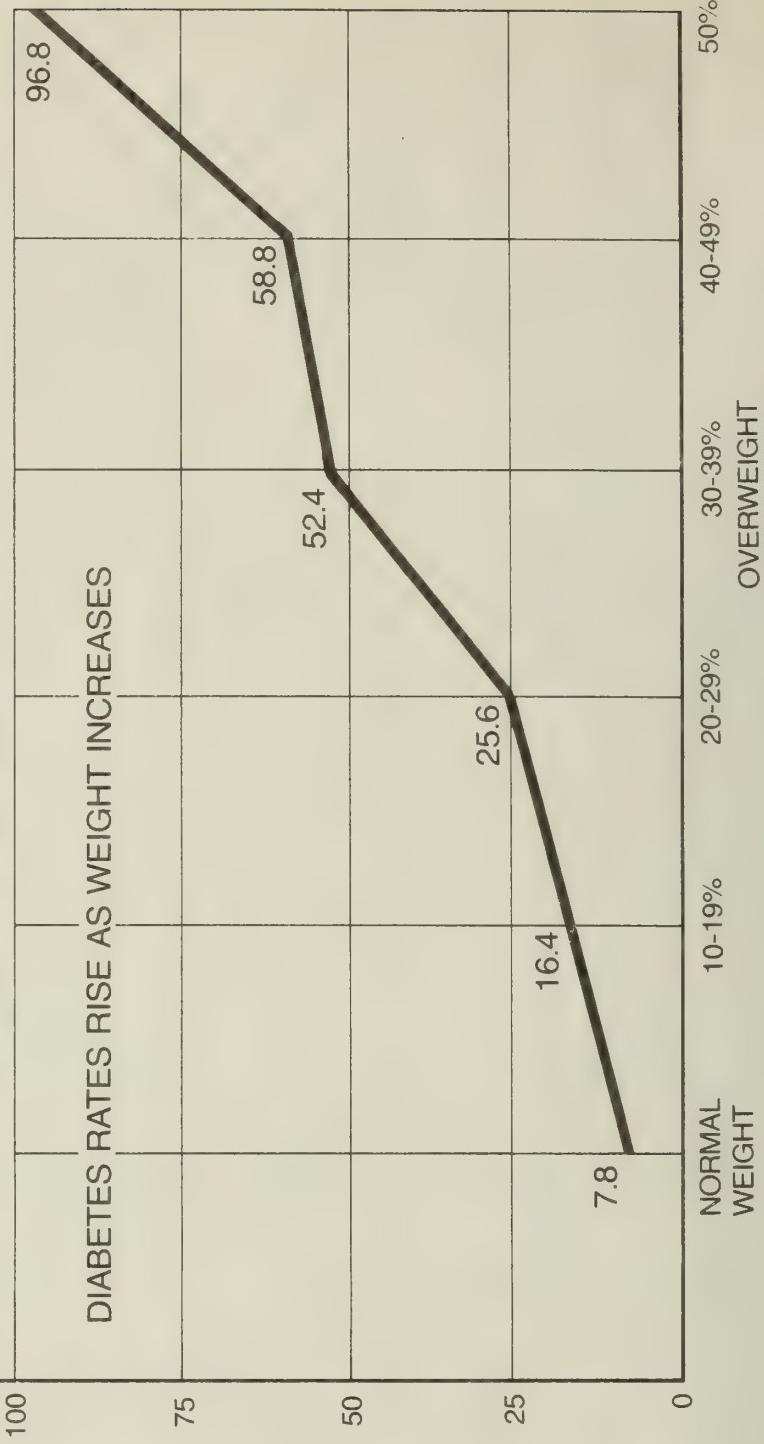
FIGURE 11

FEDERAL EMPLOYEE DIABETES SCREENING: NEW CASES PER 1,000 SCREENED, BY AGE AND WEIGHT STATUS, JULY 1963-JUNE 1964

RATE
PER 1000

RATES OF DIABETES 1½ TO 4 TIMES HIGHER AMONG OVERWEIGHT THAN NORMAL WEIGHT PERSONS OF THE SAME AGE

OVERWEIGHT 10%

NORMAL WEIGHT

AGE (YEARS)
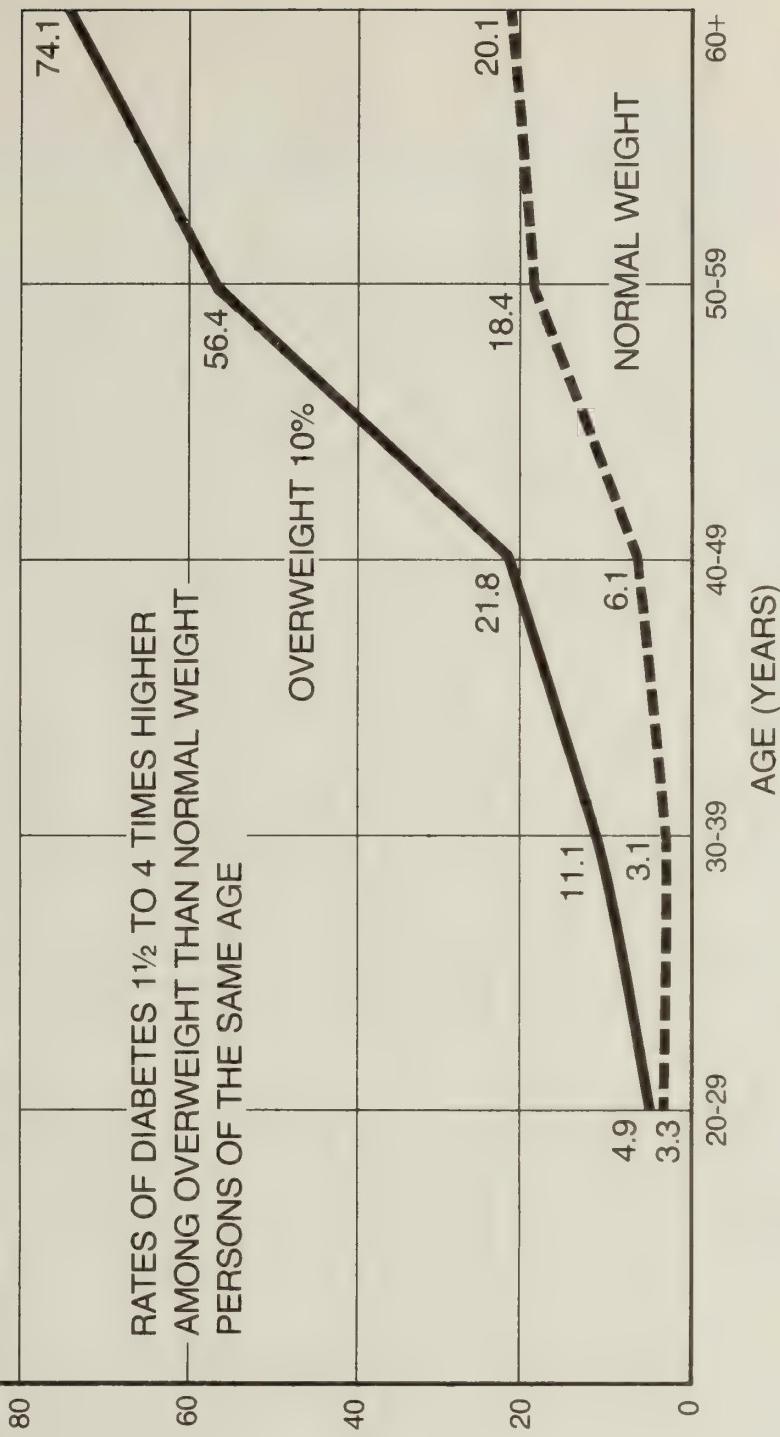
SOURCE: DIABETES AND ARTHRITIS CONTROL PROGRAM, PUBLIC HEALTH SERVICE

Severe malnutrition in childhood (as in India and Africa) is sometimes associated with an increased risk of pancreatic calcification and diabetes later in life. Excessive iron consumption may lead to diabetes, secondary to hemochromatosis. Under certain conditions, impaired glucose tolerance has been observed with deficiencies of zinc and of chromium, but it is not yet certain whether these deficiencies are significant risk factors for clinical diabetes.

The factor most strongly and consistently associated with prevalence of adult-onset diabetes is the degree and the duration of adiposity. Arguments have also been advanced that dietary sugar (2, 3) and fat (8) are especially diabetogenic. In this essay, the term "sugar" refers to all mono and disaccharides, but a substantial majority of dietary sugar is usually sucrose in those societies in which sugars furnish as much as 10% of the total calories. Increased rates of diabetes have frequently been observed in populations where sugar intake has increased (2, 3, 5, 7). It has been difficult, however, to determine whether this is a direct cause and effect relationship (5, 7, 9). These dietary changes are usually temporally related to other factors such as decreasing exercise, increases in total calories, and fat intake, among others. Moreover, no relationship could be found between the risk of diabetes and the previous sugar consumption when small groups of those with and without diabetes were studied in each of four different populations (10-13). In contrast, most intrapopulation studies showed that adiposity is a strong risk factor (5, 14). Cleave (3), with support from Cohen (2) and others, argued eloquently that a main precipitating factor in diabetes is the consumption of refined carbohydrates (both sucrose and other "refined" carbohydrates). Keen (15) thought that present evidence was not conclusive in this respect. Although West et al. found among populations a generally positive association between rates of diabetes and consumption of both sugar and fat, they also accumulated some epidemiologic evidence that is inconsistent with the hypothesis that sugar and fat are important risk factors apart from their effects or possible effects on levels of caloric consumption (4-7). Himsworth reviewed evidence that dietary carbohydrate protects against diabetes (8). In general, rates of diabetes are low where starch consumption is high (6). Trowell recently summarized evidence suggesting that, under certain conditions, the removal of fiber from flour and other foods may enhance the risk of diabetes (16).

The relative importance of sugar in determining the risk of obesity is also not well established (9,14). This may vary depending on what foods are available as replacements when sugar intake is intentionally limited or unavailable. Since refined sucrose is a concentrated and an attractive source of calories, it is widely suspected that its consumption tends to increase the risk of obesity. High rates of

besity have also been observed occasionally in populations in which
ugar consumption is low (9, 14), and in one society, fat people
robably ate less sugar than lean persons (15). High rates of diabetes
ave not been reported in any society in which obesity is rare. Investi-
ations in the laboratory give considerable support to obesity as a risk
actor. For example, obesity is associated with resistance to endoge-
ous insulin.

Cohen produced mild diabetes without producing obesity in one
roup of rats by feeding high sucrose diets (2). These diets, however,
ere much higher in sucrose (72% of calories) than those consumed by any
uman population. Moreover, obesity and diabetes have also been induced
epeatedly in animals by increasing the dietary fat. Under these condi-
ions, the percentages of calories as starch or as sugar were often
educed. In one experiment, diabetes was induced by a diet high in
rotein (17). Experiments of this kind are often difficult to interpret
ecause two or more variables are usually changed. For example, if fat
s increased, it is usually also necessary to decrease carbohydrate or
ncrease calories. In hamsters that were prone to diabetes, Gerritsen
d Dulin reduced rates of diabetes dramatically by reducing food intake
18). This was a quantitative and not a qualitative change in diet.

A review of all available laboratory and epidemiologic evidence
uggests that the most important dietary factor in increasing the risk
f diabetes is total calorie intake, irrespective of source. This still
eaves open the question of the relative importance of specific nutri-
nts such as fat and sugar in inducing excessive caloric consumption.
reviously it was commonly believed that ingestion of refined carbohy-
rates might "overstrain" the beta cells. Recent physiologic evidence
enerally tends to diminish this possibility. For example, it has been
ound that the ingestion of mixed meals containing carbohydrate, fat,
d protein stimulate beta-cell function much more strongly than carbo-
ydrate alone.

1) Complications of Diabetes:

Among populations of diabetics, substantial differences in
e frequency of certain complications sometimes occur. In Japan, for
xample, coronary disease and gangrene are much less common manifesta-
ions of diabetes than in the United States. It seems quite probable
hat the comparatively low rates of atheroschlerosis seen in the dia-
etics in many societies of Asia, Africa, and Latin America are
ttributable to their diets, which are lower in cholesterol and satu-
ated fat (both before and after discovery of diabetes). Caloric intake
s also low in relation to energy expenditure in most of these popula-
ions. Geographic and ethnic differences among populations in rates of
mall-vessel disease (glomerulosclerosis and retinopathy) are consider-
ly less. There are, however, a few societies in which microvascular

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disease seems to be less frequent in diabetics (e.g., Navajo Indians and Nigerians) (7, 19). Nutritional factors may or may not contribute to these differences. Although present data are not very satisfactory, it appears that there are differences among societies in rates of juvenile diabetes (7). Possibly, nutritional factors are influential in this respect. In Japan, for instance, marked changes in the national diet during recent years have been associated with substantial increases in rates of juvenile diabetes (20). Rates of ketosis vary among populations of diabetics, but it is not yet clear whether dietary factors play a role in these variations (1, 7).

2) Obesity and Vascular Lesions:

Vascular disease is more common in diabetic persons who have gained weight than in those who have not (21). Diabetics who have gained weight but lost it again show less frequency of vascular disease, but less in those who have lost more weight than those who lost little weight (21). Although another study of 383 diabetics revealed no relationship between atherosclerosis and obesity, Santen et al. found more obese subjects in their diabetics with arterial disease than in those without the diabetic complications (22).

Obesity is closely related to circulating triglyceride levels in both diabetics (22) and nondiabetics (23), but triglyceride levels and obesity seem to be independently related to atherosclerosis in diabetics (22). The relationship between obesity and triglyceride levels may be mediated by way of the elevated insulin levels associated with obesity (23). There is a relationship between body weight and cholesterol levels (24) with obesity associated with increased total body cholesterol synthesis (26, 27). Hypertension is also related to body weight (25, 28), and blood pressure is often reduced by weight reduction (28).

The role of obesity in the vascular complications of diabetes is not clear and the relationship may be indirect. While weight reduction results in improved glucose tolerance, lower triglyceride levels, and often lower blood pressure, it is not known if the development of atherosclerosis is slowed or reversed by this measure.

3) Summary and Conclusions:

Several nutritional factors deserve further study as to their possible role in increasing risk of diabetes, including consumption of fat, sugar, chromium, and other factors. The nutrition factor having by far the strongest relationship to diabetes is obesity. While present epidemiologic evidence is incomplete, it suggests that a substantial majority of patients with maturity-onset diabetes would never have developed diabetes had obesity been avoided. The quantitative and

qualitative effects of obesity on risk of diabetes and its complications deserve intensive study using both epidemiologic and other research methods.

Nutritional factors obviously play a major role in the etiology and prevention of macrovascular disease, the major cause of death in diabetes. Epidemiologic studies have great potential for identifying and developing preventive measures.

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d. Future Directions

1) Goal:

Although the main purpose of epidemiologic study of obesity and its relationship to diabetes will be to provide insights to facili- ate the prevention of obesity (and thus the risk of diabetes), several other potentialities for research into obesity will be outlined below.

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2) Specific Objectives:

A major objective is the systematic measurement of the many variables associated with varying degrees of leanness and obesity. While it is widely believed, for example, that sugars and starches are fattening, there is little evidence to support this notion. Examinations of hypotheses of this kind will require not only epidemiologic research, but basic and clinical investigations. On the other hand, epidemiologic studies have considerable potential in yielding clues concerning both positive and negative factors relating to risk of obesity: cultural factors, social and economic factors, exercise, dietary customs and habits, race, age, sex, occupation, psychologic factors, genetics, and other matters.

Another objective will be the study by epidemiologic methods of the effects of mitigation of obesity on diabetes and various specific complications of obesity. This will include study of the effects of both the avoidance of obesity and the reversal of obesity. Epidemiologic approaches also have some potential in the study of effectiveness in relation to cost of various strategies for achieving weight reduction.

Another objective should be the study of the factors that account for the very great variation among individuals in their tolerance obesity. Epidemiologic approaches have considerable potential when conducted in coordination with clinical and basic studies including observations of fat cell size and number, insulin secretion patterns, serum triglyceride levels, observations of weight over time, and determinations of body composition. Epidemiologic approaches also will be productive as part of investigations of the genetic background of both obesity and diabetes.

3) Approaches:

More study is needed on the degree of direct cause and effect in the very strong association between obesity and diabetes. For example, it is possible that to some degree this association is the result of low levels of exercise in both diabetic and obese persons. Basic and clinical studies will be required here, but epidemiologic approaches would also have some potential.

The epidemic of obesity in American black women deserves intensive study. Rates of obesity vary dramatically among different groups of aboriginal people including some of the Indian tribes of North America. Study of these differences among and within populations would be of interest. A major defect of previous genetic studies in diabetes has been the failure to carefully determine indices of adiposity in the probands and their close relatives. This study should include in some instances attempts to gather data on weight history over a lifetime as

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well as present weight, with, for example, determination of maximum weight or approximate maximum weight, weight at age 18, etc.

No epidemiologic studies have ever been performed on a representative group of massively obese subjects. We don't know, for example, about their weights at birth, weights of siblings and parents, patterns of the development of obesity over time, and other information. Knowledge of the specific effects of massive obesity is quite incomplete, as is information about either prevalence or incidence of diabetes in very fat persons. We know, of course, that rates of diabetes are very much higher than in the general population, but we don't know whether the lifetime incidence of diabetes in those who survive into the sixth decade would be 25%, 50%, or 75%. Study of the latter special group would have broad relevance and implication. We don't know, for example, in quantitative terms the relative importance of genetics of diabetes in determining rates of diabetes in the obese. It may be that the modest familial aspects of diabetes in the obese is attributable mainly to the familial aspects of obesity. Evidence for and against this notion can be found in the present literature, but present data are quite unsatisfactory. An epidemiologic design could be developed that would shed considerable light concerning these interrelationships. The fact that adiposity declines with old age (14) deserves further study, since it may account for the apparent sharp decline in incidence of clinical diabetes after the sixth decade.

It is widely held that obese children are much more likely to be obese as adults. This seems likely, but the amount of direct evidence to this effect is rather limited. Even if these two variables are strongly associated, it remains to be determined whether the association is largely biological or rather the result of cultural and social factors. While it has been hypothesized that susceptibility to adult obesity is enhanced by an increase in number of fat cells, generated during over-feeding in childhood, present data are by no means adequate to confirm or refute this possibility. Basic, clinical, and epidemiologic study is required.

Based on preliminary observations, it has been suggested that certain deleterious effects of obesity are more strongly associated with maturity-onset obesity than with childhood-onset obesity. This question deserves further study.

In a section above, observations were summarized on the relationship between risk of diabetes and anatomic distribution of adiposity, which should be further investigated. In certain urban societies, epidemics of obesity occur in poor teenage girls, with one study showing seven times more obesity in poor girls than in those from more affluent families. In other social circumstances, the same relationships do not prevail. These phenomena deserve further study.

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Epidemiologic methods will be applicable in the further evaluation of social and cultural factors in determining rates and extent of obesity, including studies of attitudes and concepts concerning ideal weight and the effects of these attitudes on adiposity. Epidemiologic methods have some application in the study of dietary patterns and their relationship to adiposity.

It should be kept in mind that this has not been a comprehensive list of research approaches to obesity. Here we have emphasized only those approaches having epidemiologic implications. The importance of not only obesity in the etiology of diabetes but also its many other deleterious effects requires a considerable increase in research with a variety of approaches.

4) Projects:

Detailed projects will be outlined later in this workgroup report. The discussion above suggests a number of possibilities. Studies in this field could often be an integral part of other epidemiologic enterprises, as for example, a comprehensive epidemiologic study of diabetes in a whole community. Such a study might include observations in approximately 2,000 persons with known diabetes, 2,000 with occult but clearly evident diabetes, and 2,000 with borderline or mild impairment of glucose tolerance. A sample of this size would require a community of approximately 125,000 people. In such a community or geographic region, a control group matched for age and other characteristics might be developed containing about 6,000 individuals. Thus, the size of the total group studied would be about that of the group studied in Framingham. An alternative would be to do the study in a larger population with selected samples.

One potential of such a study would be to measure in a whole population, or a representative sample thereof, many of the indices discussed above, including, for example, measurements of present and previous adiposity, genetic observations, glucose tolerance, triglyceride levels, indices of vascular disease, and other factors. In subsamples, basic and clinical investigations could be performed, some of which would relate to obesity. They might include determinations of fat cell size and number, body composition, anatomic distribution of fat, and detailed studies of serum lipids. The design might also provide for observations in two or more ethnic groups within the same community, such as blacks and whites; Indians and whites; blacks, whites, and Indians; rich and poor whites, etc. The epidemiologic aspects of such a program alone would be rather expensive, perhaps about $2 million yearly over a period of about ten years. Even so, this would be more effective in relation to cost than the support of many studies in which the quality and quantity of the epidemiologic samples were inadequate to answer some of the more urgent questions. The ongoing studies in the

Pima Indians, designed along these lines, are yielding important epi-
demiologic information. It seems likely that this information will also
have relevance for other populations. The studies are particularly rele-
vant to questions concerning the relationships between obesity and
diabetes because the Pimas are a very obese population. For several
reasons, it will also be desirable to carry out studies of this kind in
one or more other elements of the U.S. population.

2. AGING AND GLUCOSE TOLERANCE

a. Statement of the Problem

Studies in a variety of populations have demonstrated a "deteri-
oration" of glucose tolerance during the adult years of life. These
studies are largely cross-sectional; thus, age differences have been
defined but actual changes in glucose tolerance with age await study.
Two basic questions are raised by the aging effects:

1) Is the age effect physiological or normal or perhaps even
   adaptive or appropriate to other aging changes in the
   individual? If so, then normative standards (i.e., diag-
   nostic standards) should be adjusted for age.

2) Is the age effect caused by the gradual emergence over the
   years of an increasing number of true diabetics? If so,
   then diagnostic standards should not be adjusted for age.
   A combination of these two mechanisms is also possible and,
   indeed, probable.

3) References:

   1. Andres, R. Aging and diabetes. Med Clin N Am
      55:835-46, 1971.

   2. Bennett, P. H., Burch, T. A., and Miller, M. Diabetes
      mellitus in American (Pima) Indians. Lancet 2:125-28,
      1971.

   3. O'Sullivan, J. B. Age gradient in blood glucose levels;
      magnitude and clinical implications. Diabetes 23:
      713-15, 1974.

b. Impact of the Problem

The number of people in the U.S. potentially affected by the diagnostic standards dilemma is in the millions. It must be stressed that the age effect by no means involves only the aged in our society, since the impact of aging is present even as one moves from the teen years into the twenties, and is progressive throughout life. Data selected from the U.S. National Center for Health Statistics show this progression:

Age Group (yr)	Percent of subjects exceeding blood glucose of 160 mg% one hour after glucose challenge		
	Men	Women	Total
18-24	1	5	3
25-34	5	7	6
45-54	13	20	16
65-74	27	43	36
75-79	25	58	42

Thus while a relatively small -- but still very important -- percentage of young adults fail to pass a commonly applied criterion of normality on this diagnostic test for diabetes (160 mg% at one hour), the percentage of the aged who fail the test is indeed remarkable.

The impact of erroneous diagnoses of diabetes (both false positive and false negative) is potentially profound. Incorrectly identifying a person as having diabetes, aside from causing needless anguish for the patient and his family, could also result in potentially harmful therapy and important employment and insurance implications. On the other hand, the failure to detect a true case of diabetes results in the loss of opportunity to institute appropriate therapy, controversial though this therapy may be in the type of diabetic patient who requires glucose tolerance testing for diagnosis.

References:

U.S. National Center for Health Statistics. Glucose tolerance of adults, United States, 1960-62. Washington. U.S. Department of H. E. W., Public Health Service, 1964.

c. State of the Art

1) Introduction:

An extensive background is available in the methodology of
glucose tolerance testing and in the knowledge of variables other than
diabetes mellitus which influence the test. Furthermore, techniques
exist for the assessment of various "endpoints" or specific outcomes
related to the diabetic state which are applicable to epidemiologic
research. Knowledge of the impact on health of various degrees of ele-
vation of blood pressure and of obesity is far more advanced than
knowledge of the importance of different degrees of glucose intolerance
at the various ages of life. Research in progress is aimed at the
discovery of alternative means of diagnosing diabetes and at the eluci-
dation of the metabolic and hormonal variables which underlie the
development of the diabetic state and the glucose intolerance of aging.
Such research inevitably will contribute to an understanding of the age
effects on the glucose economy of the body. In addition, basic research
in the biology of aging processes will provide the essential framework
for an understanding of aging effects at a clinical level.

Research on the epidemiologic aspects of this problem will,
however, provide data obtainable in no other way. Ultimately the
question of the significance of different levels of glucose tolerance
must be answered by large-scale studies which will define in quantita-
tive statistical terms whether various levels of tolerance are or are
not harmful and whether these watershed or critical levels vary with
age.

Tables 8 and 9 provide a selective summary of a number of
studies throughout the world which demonstrate the universality of the
age effect on the one hand and the variability of the age effect in
quantitative terms on the other hand. Possible factors underlying the
differences in results among these studies include population selection
techniques, methodologic techniques in the performance of the test, and
genetic and environmental (dietary, etc.) differences among the groups
studied. This diversity is in itself an important indication for
further study.

2) Specific Techniques Available:

The extensive clinical knowledge on the diversity of manifes-
tations of the diabetic state provides the essential base for the design
of future studies. A number of techniques exist for identifying and
quantifying the development of the microangiopathy and the macroangio-
pathy associated with diabetes. Such techniques as retinal photography,
basement membrane thickness in muscle capillaries, nerve condition
velocity, creatinine clearance, and proteinuria are relatively simple,

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noninvasive, and harmless techniques -- adaptable to certain epidemiologic studies in some areas. Resting and **exercise, stress, ECG's, and** radiography of leg and other arteries are techniques which can also be applied.

Another major requirement for an epidemiologic effort is the selection of a population suitable for study. Here again experience in the conduct of long-term longitudinal studies in large populations (for example, the Framingham and Tecumseh studies) is available, along with experience in the longitudinal study of physiologic aging processes. Realistic planning based on some of the results of some studies can be expected to increase the efficiency of the experimental design for a study of the epidemiology of diabetes as related to aging. An epidemiologic age study in diabetes should also evaluate such variables as body composition and serum lipids, variables which are closely interrelated in the development of the angiopathic complications of the diabetic state. Statistical techniques for estimation of the number of subjects required, the duration of the study, and the frequency of measurement of the variables have been developed, as have the necessary techniques of multivariate analysis.

3) <u>Summary and Conclusions</u>:

   a) Uncertainty in diagnostic standards for the diagnosis of diabetes increases with advancing age.

   b) Major diagnostic errors are unquestionably being made in our current clinical practice, with the number of individuals involved in this uncertainty in the millions.

   c) Existing epidemiologic techniques can provide a rational basis for the setting of age-adjusted standards, thus increasing our understanding of the interrelations of aging processes with the processes of the disease.

4) <u>References</u>:

   1. Andres, R., Tobin, J. D., Norris, A. H., and Shock, N. W. Quantification of the rate of physiological aging in man. Proc. 10th International Congress of Gerontology, Vol. I, Plenary Sessions and Symposia. pp. 140-2, 1975.

   2. Andres, R. and Tobin, J. D. Aging, carbohydrate metabolism, and diabetes. Proc. 9th International Congress of Gerontology 1:276-280, 1972.

3. Garcia, M., McNamara, P., Gordon, T., and Kannel, W. B. Cardiovascular complications in diabetes. Adv Metab Disord 2:493-99, 1973. (The Framingham Study).

4. Ostrander, L. D., Jr. and Epstein, F. H. Diabetes, hyperglycemia, and atherosclerosis: new research directions. In: Monograph on diabetes, pp. 479-515. U.S. Government Printing Office, Washington, D.C. In press.

5. Ostrander, L. D., Jr., Francis, T., Jr., Hayner, N. S., Kjelsberg, M. O., and Epstein, F. H. The relationship of cardiovascular disease to hyperglycemia. Ann Int Med 62:1188-98, 1965. (The Tecumseh Study).

6. Schlesselman, J. J. Planning a longitudinal study. I. Sample size determination. II. Frequency of measurement and study duration. J Chron Dis 26:553-570, 1973.

d. Future Directions

1) Goal:

The purposes of future studies are (1) to define normative age standards for the diagnostic tests for diabetes mellitus and (2) to gain understanding of the interactions of aging processes with changes in glucose metabolism and other variables leading to the increase in morbidity and mortality in diabetes.

2) Specific Objectives:

One objective should be the formation of a large-scale long-term longitudinal study or studies of the natural history of the development of (1) glucose intolerance with advancing age, (2) specific pathologic changes associated with diabetes (for example, microangiopathy and macroangiopathy), and (3) mortality rates. The formation of such carefully studied cohorts will potentially also provide well-characterized volunteers across the adult age span for special studies which are too complex for large-scale study. Furthermore, the longitudinal panel would be a valuable resource for the selection of subjects with appropriate characteristics for future interventon trials.

3) Approaches:

There is indeed no alternative to the longitudinal study approach for gaining the information noted in Sections A and B above.

TABLE 8 - ORAL GLUCOSE TOLERANCE TEST

(References for this table are given in Andres and Tobin, 1972)

Study	Glucose Dose (g)	Source of Blood [d]	Age (yr) Young	Age (yr) Old	Mean Blood Gluc.[e] (mg%) One Hr Young	One Hr Old	Two Hr Young	Two Hr Old	Age Effect on glucose conc. (mg% per decade life) One Hr	Two Hr
1. U.S. Nat. Center Health Stat., 1964	50	V	18-24	75-79	100	166	---	---	12	--
2. Welborn et al., 1969	50	V	21-29	>70	86	153	---	---	10	--
3. Boyns et al., 1969	50[b]	V	<24	>55	89	125	74	78	9	1
4. Nilsson et al., 1967	(50)[b]	C	20-39	60-79	111	154	---	---	11	--
5. Butterfield, 1966	50	C	20-29	70-79	125	194	86	121	14	7
6. Diabetes Survey Working Party, 1963	50	C	<29	>70	122	186	98	119	13	4
7. Hayner et al., 1965	100	V	16-19	70-79	100	177	---	---	13	--
8. Unger, 1957	100	V	18-29	50-59	---	---	99	131	--	11
9. Studer et al., 1969	100	C	25-34	65-74	---	---	98	127	--	7
10. Gerontology Research Center, 1972	(122)[c]	V	20-29	70-79	144	174	113	145	6	6

[a] In studies 3-6 and 8-10, glucose was ingested in the morning after an overnight fast. In studies 1, 2, and 7 subjects presented themselves for testing at various times of the day and at various time intervals after the last meal.

[b] 30 G glucose per M^2 surface area - 50 g for man of average size

[c] 1.75 g per kg body weight = 122 g per 70 kg man

[d] V = antecubital venous blood; C = capillary blood

[e] It should be stressed that these values should not be taken as the upper limits of normality. They represent mean values. Note that at two hours the mean value for the old subjects is equal to or exceeds 120 mg%, a

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(References for this table are given in Andres and Tobin, 1972)

		Age of Subjects[a]		Mean Decay Constant, K[b]		Age Effect on K (percent per decade of life)[c]
Study	Glucose Dose	Young	Old	Young	Old	
1. Schneeberg & Finestone, 1952[d]	0.33g/kg	16-39(48)	60-90 (39)	1.88	1.14	0.15
2. Conard, 1955	0.33g/kg	20-39(33)	60-88 (27)	1.85	1.09	0.19
3. Silverstone et al., 1957	25g	23-37(12)	65-87 (11)	1.68	0.98	0.15
4. Streeten et al., 1964	25g	21-32(23)	70-92 (15)	2.35	1.16	0.21
5. Dyck & Moorhouse, 1966[e]	$50g/1.73m^2$	18-39(31)	60-75 (13)	2.61	1.48	0.28
6. Cerasi & Luft, 1967[f]	25g	20-39(49)	60-79 (14)	1.76	1.45	0.09
7. Gerontology Research Center, 1972	0.375g/kg	20-39(70)	60-79(111)	1.37	1.01	0.09

[a] The number of subjects in each age group is given in parentheses.

[b] The decay constant is computed from the absolute glucose concentration, not from the increment in glucose over the fasting value. K has the dimensions of percent glucose disappearance per minute.

[c] Computed from the difference between mean K of the young and old groups divided by the difference between the mean age of these two groups, multiplied by 10.

[d] K values computed from table of mean glucose concentrations at 30 and 60 minutes.

[e] The higher mean K values in this study are due to the high glucose dose used. The authors consider the limit of normality to be 1.50 with this dose.

[f] The high mean K value in the older subjects in this study is at least partly due to the elimination of subjects with $K < 1.00$; the authors wished to study "normal" old subjects. The mean is thus arbitrarily raised.

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3. PARITY AND DIABETES

    a. Statement of the Problem

        In most populations the proportion of the females with diabetes
is greater than that of males.

    b. Impact

        An understanding of the reasons for the apparently excessive
proportion of females with diabetes might increase knowledge about the
causes of diabetes which might allow preventive measures to be taken.

    c. Hypothesis

        The hypothesis that the higher prevalence of diabetes among
women is attributable to the recurrent metabolic stresses of pregnancy
was advanced many decades ago, based on the recognition that changes in
glucose tolerance occurred frequently during pregnancy.

        The concept was supported by several groups of investigators
(1-4), although methodologic problems raised questions about the valid-
ity of the conclusions, primarily because adequate control groups were
not usually available.

        The question was re-examined using U.S. National Health Exami-
nation Survey data. These data appeared to show a relationship between
parity and evidence of stated diabetes. Among persons without known
diabetes who received a glucose tolerance test, however, no clear
relationship emerged; yet a trend toward high glucose levels in the
highest parity groups was apparent, although the report concluded that
no definite relationship was established.

    d. Future Directions

        Re-examination of the question in large samples of the popula-
tion -- sufficient to allow for the simultaneous subdivision into age,
race, and degree of obesity -- is required if this question is to be
resolved. It appears that the inclusion of appropriate data in the
National Health Interview Survey and Health Examination Surveys would
permit further exploration of this question without additional resource
except those necessary for a pertinent analysis of these data.

    e. References

        1. Murro, H. W., Eaton, J. C., and Glen, A. Survey of a
            Scottish diabetic clinic. J Clin Endocrinol Metab
            9:48, 1949.

1:818, 1950.

3. Fitzgerald, M., Malins, J., O'Sullivan, D., and Wall, M. The effect of sex and parity on the incidence of diabetes mellitus. Quant J Med 117:57, 1961.

4. Hoet, J. P. and Lukens, F. D. W. Carbohydrate metabolism in pregnancy. Diabetes 3:1, 1954.

5. National Center for Health Statistics: Child bearing and diabetes mellitus. Vital and Health Statistics #PHS Pub No. 1000-Series 11, No. 18, Public Health Service, U.S. Government Printing Office, Washington, D. C.

4. GEOGRAPHIC AND RACIAL FACTORS

a. Statement of the Problem

Numerous prevalence studies of diabetes have served to define partially the variation in the prevalence of diabetes in many parts of the world. These investigations have taken place mainly over the past twenty years (1). True comparisons have been limited, however, by the great variations in the methodologies employed, so that relatively little information concerning the etiology and pathogenesis of diabetes has emerged. An enormous range in prevalence even within single racial groups has been found. For example, Athabaskan Indians in Alaska (2) and Pima Indians (3) of Arizona have an approximately 50-fold variation.

The magnitude of such variation indicates that clues to etiology could be found by careful comparisons of the frequency of relevant variables so that etiologic factors could be identified and their importance quantified.

b. Impact

Knowledge of disease prevalence, establishment of the relative importance of known etiologic factors, and the identification of new factors of possible etiologic significance are important. They could help serve as a basis for planning preventive measures, would focus specific investigations on the possible mechanisms underlying the associations, and could produce hypotheses to test for causal and noncausal relationships.

c. State of the Art

Within the United States, prevalence data concerning the frequency of diabetes in specific subgroups of the population is either

scanty or completely lacking. For example, no satisfactory data exist on the frequency of diabetes among Mexican-Americans and Orientals (e.g., persons of Chinese, Japanese descent) within the United States. Such data, especially if comparable data from persons of similar age, etc., in their homelands were available, would facilitate determination of the roles of diet, obesity, change in life style, and other factors in the etiology of diabetes mellitus. Large variations have already been demonstrated in the American Indian, but investigations of the factors underlying this variation have been only superficial to now (3).

Also it is not known how the course, complications, and mortality from diabetes among subgroups of the United States population compare with the same factors for persons with diabetes of the same ethnic origin in the homelands, although there are some data to suggest that the patterns of complications are different in the two groups.

d. Future Directions

1) Goal:

A primary goal is to gain insight into factors which determine the prevalence of diabetes in different racial groups living in similar and different environments.

2) Objectives:

No single approach will serve to elucidate all existing questions in this area, but the continuation of specific epidemiologic studies designed to identify or quantify specific hypotheses should be encouraged, with the assurance that useful hypotheses will be subjected to more vigorous hypothesis testing -- often by longitudinal studies.

Such studies require that expertise and competence in the field of epidemiology, particularly with special emphasis on diabetes, should be fostered and developed, and that the opportunities for useful work in this field be made available.

Such studies require that funding be available for such activities, which may involve work both in the United States and abroad, and the value of each approach should be individually reviewed and appraised on its merits.

Fellowships in Epidemiology should be established on a recurring basis for a limited number of qualified persons with a specific interest in diabetes to develop sufficient manpower to undertake such studies in the future.

3) References:

1. The epidemiology of diabetes. In: Ostman, J., ed. Proceedings of the Sixth Congress of International Diabetes Federation. pp. 651-700.

2. Mouratoff, G. J., Carroll, N. V., and Scott, E. M. Diabetes 18:29, 1969.

3. Bennett, P. H., Rushforth, N. B., Miller, M., and LeCompte, P. E. Epidemiological studies of diabetes in Pima Indians. Recent Prog Horm Res 32:1975 (in press).

5. OTHER ETIOLOGIC FACTORS, E.G., FAMILY INCOME, RACE, FAMILIAL AGGREGATIONS, AND TIME

a. Statement of the Problem

The prevalence of diabetes varies with factors such as family income and socioeconomic status. It is uncertain to what extent these associations are attributable to obesity and racial factors and/or whether the racial factors are attributable primarily to genetic or environmental determinants. Also an enigma is whether the familial aggregation of diabetes primarily results from genetic determinants or whether the similarity of environment shared by family members is to a greater or lesser degree responsible for the familial clustering of diabetes.

The prevalence of reported diabetes has increased considerably within the United States between 1965 and 1973, especially among older females and among nonwhites.

b. Impact

The prevalence and incidence of reported diabetes show a recent and alarming increase in the United States, a trend which may represent more complete casefinding or may represent, at least in part, a true increase in frequency.

c. State of the Art

In the United States, diabetes and obesity are more frequent among nonwhites, and also more frequent among those with lower family income. Additional data are required to determine if these ethnic and economic associations are entirely due to the link between diabetes and obesity, or if there are independent effects of race and income which cannot be explained on the basis of obesity.

More information, collected in a standardized form, is necessary to determine whether the observed increase is due to more complete case-finding, or whether the increase is actually occurring -- and, if so, to what extent this may be attributed to changes in age, obesity, or other possible environmental agents, since genetic factors cannot be invoked.

d. Future Directions

Future data concerning diabetes within the United States should be collected in such a way as to make possible analyses to examine the extent to which the variables of diabetes, obesity, income, race, and changes with time are independently determined.

Additional specific hypothesis-testing studies are required to determine the relative importance of environmental and genetic factors in the familial aggregation of diabetes and to determine whether the higher prevalence of diabetes in nonwhites has primarily a genetic or an environmental basis. Many possible approaches to these complex questions may be made, and no single approach will provide data which will answer all the specific questions.

D. DIABETES CASEFINDING

1. STATEMENT OF THE PROBLEM

Casefinding has attracted a great deal of attention from doctors and lay persons for many years. The possibility of identifying individuals in the early stages of diabetes and starting treatment when the disease could be ameliorated and its complications prevented is most attractive, especially when only at most palliative treatment is available for the severely disabling complications, such as diabetic blindness, neuropathy and amputation, and for potentially fatal complications of diabetic keto-acidosis, hyperosmolar coma, renal failure, and coronary heart disease (1).

Casefinding in diabetes is particularly worthy of consideration since the disease, especially in the adult, is frequently asymptomatic and may remain so for years (2).

2. IMPACT OF THE PROBLEM

If diabetes could be detected at a stage before which symptoms or the chronic vascular complications become apparent, and if adequate methods of preventing the development of the complications were available, the public health and individual benefit would be enormous. Lesser, but nevertheless, significant goals include the prevention of diabetic keto-acidosis and hyperosmolar coma, prevention of the

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complications of diabetic pregnancy which affect both the mother and her offspring, and the modification of the course of the asymptomatic diabetic to prevent the development of acute symptoms such as polydypsia, polyuria, and weight loss.

Asymptomatic unrecognized diabetes probably exists in up to 4% of the U.S. population aged 18 years and over (3), since this proportion of the adult population has been demonstrated to have glucose levels $\geq$ 200 mg/100 in one hour after a 50 g. glucose load.

3. STATE OF THE ART

Suitable methods to test and identify asymptomatic diabetic subjects exist, the most useful test involving the administration of an oral glucose load and a plasma glucose determination one or two hours after consuming the load. While the specific glucose levels to determine the presence of diabetes are much debated, in most individuals it is often possible to arrive at a diagnostic decision on the basis of the usual screening tests, followed by a more specific diagnostic test for subjects who have abnormal screening tests.

The major problems associated with the promulgation of casefinding activities revolve around the questions:

a. Can the evolution of asymptomatic disease into symptomatic diabetes be prevented by safe acceptable and effective medical (and for practical purposes -- dietary) management?

b. Does early diagnosis and appropriate management prevent the development of keto-acidosis or hyperosmolar coma sufficiently often to make casefinding cost-effective?

c. Do any of the available and acceptable methods of management lead to the delay in onset or possibly prevent the chronic vascular complications?

d. In pregnant women, does early diagnosis lead to improvement in the course or outcome of pregnancy?

4. CASEFINDING IN PREGNANCY

Evidence of benefit from casefinding activities is more convincing in pregnant women than in other groups. There is, however, a dearth of relevant information concerning the value of casefinding in other groups.

O'Sullivan et al. (4) have demonstrated that high risk pregnancies can be effectively identified by blood sugar determination following an oral glucose load. Furthermore, O'Sullivan and other co-workers (5)

found evidence in two studies that treatment with insulin appeared to be effective in reducing the proportion of large babies and viable losses in women with gestational diabetes. Neither study was individually significant, but the pooled data indicated a statistically significant effect.

5. CASEFINDING IN OTHER GROUPS

Since data are lacking on the possible long-term benefits of casefinding in other persons, it is sometimes recommended without adequate scientific justification that casefinding is a useful activity in the obese, in close relatives of diabetics, and in the elderly -- and as part of routine medical examinations.

The value of earlier diagnosis in these groups needs to be ascertained, along with the further investigation of the questions of whether the chronic vascular complications are related to the level of glucose intolerance in the asymptomatic diabetic person and whether or not conventional diagnostic levels are optimal for the identification of persons at risk of developing the long-term complications of diabetes.

6. FUTURE DIRECTIONS

Goal A. To determine the benefits of diabetes casefinding. Since the benefits of recognition of high risk pregnancy are considerable and wide ranging, it is recommended that all pregnant women and especially those aged 25 and over be screened for diabetes during pregnancy.

Goal B. It is important to confirm that the treatment of gestational diabetes does indeed improve the outcome of pregnancy, and it is recommended that a further randomized controlled clinical trial be conducted, on a larger scale than heretofore.

Goal C. To determine the medical and social value of casefinding in other groups. Controlled trials of the effect of early, especially dietary, treatment of asymptomatic diabetes should be performed to determine if the rate of progression to symptomatic diabetes can be reduced and, if so, whether this mode of management can reduce or delay the appearance of the serious vascular complication of diabetes and reduce mortality. If this reduction occurs, then the importance and extent of diabetes casefinding will be redefined.

7. REFERENCES

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E. RECOMMENDATIONS: PROJECT SUMMARY SHEETS

Project Titles

1. National Diabetes Data Council

2. Guidelines for Diabetes Source Book

3. Health Statistic Data Library

4. Diabetes Mortality Statistics

5. Death Certificate Linkage

6. Age and Diagnostic Standards for Diabetes

7. Early Treatment of Asymptomatic Diabetes

8. Improving the Outcome of the Asymptomatic Diabetic Pregnancy

9. The Causes and Effects of Diabetes in the General Population

PROJECT SUMMARY SHEET

PROJECT TITLE: NATIONAL DIABETES DATA COUNCIL

OBJECTIVE: To assure that data about diabetes of public health con-
                  cerns be collected, integrated and disseminated.

APPROACH TITLE:

   Diabetes data council to foster collection, integration, and dis-
   semination of vital and health statistics related to diabetes.

DESCRIPTION OF PROJECT:

   A permanent data council as established by law in an appropriate
   Federal structure with a chairman who is responsible for publishing
   every five years a diabetes source book (as described in Project
   Summary Sheet "Diabetes Source Book") and who is responsible for
   promoting appropriate data collection and analysis.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Permanent establishment with adequate staffing and funding
       (legislate?).
   2. Chairman be appointed on merit by lawfully constituted govern-
       ment body responsible for public health data, (example, National
       Committee for Vital and Health Statistics) and be personally
       responsible for the "Source Book."
   3. Data council to be appointed by the chairman and include repre-
       sentation from government data collection agencies and data
       producing (service statistics) agencies; from public and private
       service agencies who will use the data; and from the public --
       all members should have some credentials related to diabetes.

INPUT REQUIRED:

   Salary for 15% time chairman. Staff and funds necessary to hold
   meetings of data council and subordinate workgroups. Staff and
   funds necessary for compilation and publication of "Source Book."
   Some funds for contracting for analysis of data collected by non-
   government agencies.

FORM OF RESULTS:

Diabetes Source Book (see project summary sheet "Source Book").
Recommendation to government agencies as to type of data to be
collected and its analysis.

PROJECT SUMMARY SHEET

PROJECT TITLE: GUIDELINES FOR DIABETES SOURCE BOOK

OBJECTIVE: Assure that data about diabetes be collected from public health concern, integrated and then disseminated.

APPROACH TITLE:

Working group to set guidelines for a Diabetes Source Book

DESCRIPTION OF PROJECT:

The data council would address the vital and health statistics related to diabetes by asking the following questions in the following order:
a) What purpose will the knowledge serve? Example: planning of services, patient counseling, assignment of national priority, etc.
b) Specific hypothesis testing question related to purpose.
c) Data presentation necessary for hypothesis testing, tabulation, analysis and interpretation.
d) Recommended improvement in type and quality of data collection and analysis and suggested mechanisms to implement recommendations.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

1. Constitution of workgroup.
2. Provision of funds and personnel to support workgroup activities.

PRESENT STATUS:

A beginning has been made in various workgroups to compile statistics about diabetes. The purpose of each compilation has, however, not been specified so that the utility of this data is limited.

INPUT REQUIRED:

See key events.

Guidelines to the quinquennial diabetes source book production
task force to help structure the first source book produced by the
data council.

PROJECT SUMMARY SHEET

PROJECT TITLE: HEALTH STATISTICS DATA LIBRARY

OBJECTIVE: To establish a library of data relevant to diabetes and
                 other acute and chronic diseases to enable access to
                 already existing and future data such as that collected
                 in the National Health Interview and National Health
                 Examination Surveys.

DESCRIPTION OF PROJECT:

    To establish a library for public access containing data tapes and
    necessary documentation of health related data, to be made available
    as a service to interested investigators and agencies.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Willingness of agencies to provide "clean" data tapes and docu-
        mentation concerning the sources and nature of the data.
    2. Facilities to copy data tapes and documents at a reasonable cost.
    3. Staff and funds necessary to continually maintain and update the
        library.
    4. Publicize the availability of specific data sets, especially of
        additions, as they become available.

PRESENT STATUS:

    Limited (and delayed) access to selected data collected by National
    Center for Health Statistics.

INPUT REQUIRED:

    Directives to appropriate data collection agencies to supply appro-
    priate information for public usage.

FORM OF RESULTS:

    Better reporting of Health Statistics, and alternative analyses
    which would more fully exploit existing resources.

PROJECT SUMMARY SHEET

OBJECTIVE: To tabulate both underlying and contributing causes of
                 death in relation to age, sex, race, etc.

APPROACH TITLE:

   Diabetes Mortality Statistics

DESCRIPTION OF PROJECT:

   Diabetes mortality statistics are severely limited by the current
   practice of tabulating only underlying cause of death in conventional
   tabulations. The addition of tabulations by contributing causes
   would considerably increase our knowledge of the impact of diabetes
   (and other chronic diseases) on health.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Multiple cause coding necessary.
   2. Analysis of multiple causes of mortality in meaningful ways.
   3. Availability of sufficient personnel and other resources at
       National Center for Health Statistics.

PRESENT STATUS:

   Only one attempt to do this has been made. This was done in
   1955 and proved the feasibility and desirability of this approach.

INPUT REQUIRED:

   Presently existing death certificates. Additional personnel and
   resources to National Center for Health Statistics.

FORM OF RESULTS:

   More informative Mortality Statistics in Diabetes and other chronic
   diseases.

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PROJECT SUMMARY SHEET

PROJECT TITLE: DEATH CERTIFICATE LINKAGE

OBJECTIVE: Promote understanding of natural history of diabetes by
                 longitudinal cohort studies.

APPROACH TITLE:

     Linkage of death certificates with data collected by agencies con-
     strained to confidentiality by law (Bureau of Census, National Center
     for Health Statistics).

DESCRIPTION OF PROJECT:

     Persons must have a common identifying characteristic in surveys
     during life and at death.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

     1. Implementation of identifying systems
     2. Ensure confidentiality of data so that individuals once linked
         cannot be identified to their or their families detriment.

PROJECT SUMMARY SHEET

PROJECT TITLE: AGE AND DIAGNOSTIC STANDARDS FOR DIABETES

OBJECTIVE: To define normative standards for the glucose tolerance
                 test and to define in quantitative terms the effect of
                 such variables as aging, obesity, dietary factors, and
                 activity levels on the natural history of the develop-
                 ment of diabetes in the population.

APPROACH TITLE:

    A long-term longitudinal multi-disciplinary study to define normative
    age-adjusted diagnostic standards for diabetes.

DESCRIPTION OF PROJECT:

    Cohorts covering the entire age range and both sexes will be selected
    so as to provide appropriate numbers of subjects in the borderline
    range of glucose tolerance along with appropriate controls. Subjects
    will agree to participate in a long-term (10-15 year) longitudinal
    study with periodic testing for diabetes and for the known "end-
    points" of the diabetic state, the micro- and macro-angiopathies.
    Variables known or suspected to have an impact on the development of
    the disease or its complications (obesity, diet, activity, etc.) will
    be assessed.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Identification of principal investigator and institution to pro-
        vide continuity over a 10-15 year period.
    2. Assurance of long-term funding.
    3. Selection of stable population.
    4. Assembly of multi-disciplinary team to measure and evaluate the
        progression and outcome.

PRESENT STATUS:

    1. Extensive background in the technical complexities of glucose
        tolerance testing is available.
    2. Experience in unique problems of the conduct of longitudinal

studies has been gained.

3. Noninvasive quantitative techniques for the assessment of the clinical endpoints of the diabetic state have been developed (e.g., retinal photography, basement membrane thickness, renal function, exercise electrocardiography).

INPUT REQUIRED:

Scientific, administrative, and technical staff for a large scale multi-disciplinary population study must be developed. Population base must be selected from among a variety of possibilities (extension of current longitudinal studies, veterans hospitals, armed services, employees of large companies, health plan enrollees, etc.)

FORM OF RESULTS:

Computer-based data storage system will provide direct actuarial analyses (e.g., mortality rates of specific age groups with varying glucose tolerance characteristics and similar data for morbidity rates of the diabetes-linked angiopathies). In addition, the interactions of such "risk-factor" variables as age, obesity, dietary characteristics, activity levels, and metabolic and endocrine factors in the development of the overt diabetic state will be quantified.

PROJECT SUMMARY SHEET

PROJECT TITLE: EARLY TREATMENT OF ASYMPTOMATIC DIABETES

OBJECTIVE: To determine whether dietary treatment of the asympto-
                 matic previously unrecognized diabetic can (a) delay or
                 prevent progression to symptomatic diabetes (b) reduce
                 or delay the appearance of the complications of diabetes
                 and (c) reduce mortality from diabetes.

DESCRIPTION OF PROJECT:

   Following identification of large numbers (perhaps 500) asymptomatic
   previously unrecognized diabetics, subjects would be randomized into
   two groups -- a control, who would receive no special attention, and
   a dietary treatment group who would be given detailed dietary advice.
   Both groups would be followed periodically for up to 25 years.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Adequate long-term follow up to monitor (a) development of
       symptoms (b) appearance of vascular complications and (c)
       mortality.
   2. Casefinding activities in a sufficiently large relatively stable
       population of adults.
   3. Long-term funding.

PRESENT STATUS:

   Only the UGDP study has made any attempt to conduct a randomized
   controlled clinical trial among asymptomatic diabetics. The con-
   tinuation of this study is important to assess the effects of drug
   therapy (i.e., insulin vs. placebo on the rate of development of
   vascular complications and mortality) to enable better description
   of natural history of diabetes and the possible benefit or harm of
   insulin therapy.

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The identification of a sufficiently large stable population of otherwise previously unrecognized diabetics.

1) Description of the natural history of glucose intolerance, symptomatic **diabetes,** and natural history of the complications.
2) Indicators of the value of early recognition and dietary treatment of diabetes.
3) With a slight addition by following in a similar manner of a sample of subjects with glucose tolerance within the normal range, the prognostic significance of the glucose tolerance test and its relationship to outcome could be defined.

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PROJECT SUMMARY SHEET

PROJECT TITLE: IMPROVING THE OUTCOME OF THE ASYMPTOMATIC DIABETIC
                 PREGNANCY

OBJECTIVE: To confirm the value of insulin treatment of asymptoma-
                 tic or gestational diabetes in pregnancy.

APPROACH TITLE:

    Insulin treatment in asymptomatic diabetes in pregnancy.

DESCRIPTION OF PROJECT:

    Systematic glucose tolerance testing in pregnancy will identify
    asymptomatic (mild) diabetes, and appears to identify a group of
    high risk pregnancies.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Routine glucose tolerance testing and the identification of
        several hundred pregnant women with asymptomatic diabetes.
    2. Randomization of such women into treatment and control groups.
    3. Measurement of parameters of the outcome of pregnancy.

PRESENT STATUS:

    Two earlier studies have both suggested improvement in the outcome
    of pregnancy when insulin treatment has been administered to the
    mother. The practice of treating such women is not widely followed
    and benefit has not yet been proven in a totally satisfactory manner
    and has not been independently confirmed.

FORM OF RESULTS:

    Improved outcome, i.e., reduced morbidity and mortality, of the
    asymptomatic (frequently unrecognized) diabetic pregnancy.

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PROJECT SUMMARY SHEET

PROJECT TITLE: THE CAUSES AND EFFECTS OF DIABETES IN THE GENERAL
                 POPULATION

OBJECTIVE: To achieve understanding of etiology, natural history of
                 diabetes, and its vascular complications.

APPROACH TITLE:

   Comprehensive multifaceted study in a community of diabetes and its
   complications, and of factors relating thereto.

DESCRIPTION OF PROJECT:

   In a general population of approximately 100,000 persons, subjects
   with diabetes (known and occult), those with varying degrees of glu
   cose tolerance, and a subsample of those with normal glucose toler-
   ance will be studied. Each group will be examined for baseline
   characteristics including: age, height, weight, indices of adipos-
   ity, serum lipids, blood pressure, smoking, insulin levels, diet,
   indices of vascular status, including EKG's, peripheral vascular
   parameters, and microvascular disease, including retinal and renal
   examinations, and in subsamples status of glucose tolerance and
   adiposity of close relatives. Certain examinations will be repeate
   periodically on a long-term basis. A byproduct of this study would
   be the potentiality for related basic and clinical investigations.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1.   Identification of suitable population, resources, and personnel.
   2.   Draw up detailed protocol for each of various elements of study
   3.   Assurance of long-term stable funding.

PRESENT STATUS:

   Only the present studies of the Pima Indians are in any way compar
   able in scope and character to the proposed project. Because of t
   size and character of the population samples proposed, the finding
   would yield information more broadly applicable to the general
   population.

Adequate long-term funding, high degree of community cooperation and a stable team of well-qualified investigators and supporting person-nel. Estimated cost of $1.5 million per year over minimum of ten years.

FORM OF RESULTS:

New knowledge on epidemiology, **etiology,** and natural history and impact of diabetes and its complications.

F. APPENDIX

EPIDEMIOLOGICAL STUDIES OF DIABETES IN THE PIMA INDIANS

by

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Epidemiologic methods are used increasingly to define and attack the problems associated with chronic disease. Especially when applied longitudinally to natural populations, such techniques may lead to better understanding of disease causation, etiology, and natural history, and may offer approaches to the prevention of the disease itself, or to the modification of its course. The epidemiologic method has been particularly useful in relatively common diseases, yet there have been few prospective epidemiologic studies of diabetes mellitus.

In 1963, a field study was undertaken in the epidemiology of rheumatoid arthritis, on the Gila River Indian Reservation in south-central Arizona, the home of the Pima Indians. The Pima Indians and their ancestors have resided in this region of the hot dry Sonoran Desert for at least two thousand years cultivating crops by judicious use of irrigation from the Gila River; the majority of the Pima still reside in the area (Haury, 1967; Quilliam, 1972; Cain, 1972). During the survey, a large proportion of the adult respondents stated that they had diabetes, as others had reported (Cohen, 1954; Parts et al., 1961), and the available blood sugar determinations appeared to confirm this fact.

To follow up the initial impressions and to document more adequately the prevalence and major characteristics of the disease among the Pima, a formal study of diabetes was initiated in 1965. An extraordinarily high prevalence of hyperglycemia was found, and the specific complications of diabetes, such as retinopathy, were found in abundance. Consequently, a long-term prospective study was initiated in which every resident of the Sacaton Service Unit of the reservation, aged five years and over, was asked to participate in examinations at intervals of two years.

The major aims of the study have been

1) to describe the prevalence and distribution of diabetes in the community.

2) to determine the occurrence and distribution of the diabetes-related sequelae, especially the vascular complications.

3) to attempt to identify the factors leading to the development of glucose intolerance.

4) to identify factors associated with the development of the complications of diabetes.

The biennial examination of each subject has included a modified glucose tolerance test, tests of renal function, retinal examinations, and -- in those aged 15 and over -- electrocardiograms, radiographs of the chest and soft tissues of the thigh and calf, and retinal photographs.[1] A glucose tolerance test using an oral 75 gm glucose equivalent carbohydrate load[2] has been given to each subject on each examination regardless of the time of the previous meal. Two hours later, venous blood was drawn for the measurement of the plasma glucose concentration on the AutoAnalyzer, using the modified Hoffman method.[3] Serum creatinine and cholesterol were determined on an additional serum sample. Since 1967, one-hour glucose determinations have also been made routinely in subjects aged 15 years and over.

Before drinking the carbohydrate load, each subject was asked to void, and two hours later a urine sample was collected, which was tested for protein and glucose with dipsticks.[4] Whenever protein was found in a concentration of approximately 30mg/100ml or more ($\geq$ 1+), a quantitative determination of the protein concentration and creatinine concentration in the urine was made. Carefully selected samples of the population have also received a variety of other diabetes-related tests.

Post mortem data have been collected whenever possible on members of the Pima Indian population who died since our initial survey in 1965, and selected characteristics have been sought in earlier autopsy material, i.e., since 1961. Death certificates have been collected systematically since 1964.

A private census of the geographically-defined study area of the Gila River reservation was undertaken. As of 1 January 1966, there were 3,035 half- to full-blooded Pima Indian residents aged five years and over, of whom 2,491 (82%) received a glucose tolerance test during the baseline examination period (2/1965-2/1969). In addition, 426 other Pima Indians, who became five years of age or who returned to reside on the reservation, were also examined prior to the end of the baseline period.

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[1] Initially a one-in-two sample of those aged 30 years and over received these examinations but after examination of the first 1,100 persons, all those examined aged 15 years and over received them.

[2] Glucola, Ames Company, Elkhart, Indiana, or Dexcola, Custom Laboratories, Baltimore, Maryland.

[3] Technicon AutoAnalyzer Method File N-20, Technicon Instruments Corporation, Chauncey, New York, 1965.

[4] Labstix, Ames Company, Elkhart, Indiana.

The glucose-tolerance results by sex and age group at the time of the first examination are shown in Table 1. For the purpose of defining prevalence, initially those subjects with a two-hour post-load glucose level of $\geq$ 160mg/100ml or unequivocal previous evidence of glucose intolerance were considered to have diabetes. The criterion is arbitrary and corresponds to a whole-blood glucose level of approximately 140mg/100ml. This represents a conservative criterion in relation to the 120mg/100ml post-load blood glucose value sometimes used for diagnosis.

The age-specific prevalence of diabetes rose as age increased to 47% in the 65-74 year old males and to 69% in the 55-64 year old females, and then fell in the older age groups. The prevalence in females was higher than in males beyond 35 years of age (p < 0.001). Below this age, the prevalence in the two sexes was rather similar, although the females did have a significantly higher rate in the 5-14 year age-group (p < 0.01; Bennett et al., 1971).

Half of those with two-hour glucose levels of $\geq$ 160mg/100ml had been recognized to have diabetes mellitus prior to this study, mainly as a result of presentation for medical care with the usual spectrum of classical symptoms. Eleven of these 279 subjects had lower two-hour glucose levels, but had either taken hypoglycemic medication shortly before the tolerance test or had unequivocal evidence of previous glucose intolerance.

Age at Diagnosis

The majority of the 279 subjects with an established diagnosis had been first recognized to have diabetes between the ages of 25 and 64 years. When related to the population at risk, the modal age at diagnosis was between 45-54 years. Among those examined, no previously known cases had been recognized below ten years of age, but 14 (5%) had presented before the age of 25 years.

Treatment

Eighty-five percent of the previously recognized diabetics had received specific hypoglycemic medication by the time of this study. Thirty-nine percent of the males had received insulin, and 41% only oral hypoglycemic agents. Of the females, 60% had taken insulin, and 7% had been treated with oral agents only.

Even before systematic glucose-tolerance testing, some 10% of the Pima aged five years and over and 29% of those aged 35 years and over

were recognized as having diabetes mellitus. Following systematic glucose-tolerance tests, the Pima Indians showed an overall prevalence of diabetes of 50% among those aged 35 years and over. Significantly higher than any previously reported, these rates are at least ten times greater than those generally estimated for the prevalence of diabetes among the same age-groups in western Europe and the United States.

Estimates of the prevalence of diabetes in western Europe and the United States generally range between 1% and 3% (Jorde, 1969; Wilkerson et al., 1947). Studies employing a glucose-tolerance test yield general ly higher prevalences; and in Bedford, England, and Sudbury, Massachu- setts, the use of a two-hour blood sugar of 120mg/100ml as a diagnostic criterion, after glucose loads of 50 gms and 100 gms respectively, led to prevalence estimates of approximately 10% (Butterfield, 1964; O'Sullivan, 1969). High rates have also been recorded among some other ethnic groups -- for example, the urbanized East Indian population in Cape Town, South Africa (12.6% aged 35 and over), (Marine et al., 1969) the New Zealand Maori (5% aged 20 years and over), (Prior et al., 1966), and native Hawaiians (7.8% in adults) (Sloan, 1963).

Diabetes Prevalence in Other American Indians

In contrast to the Pima, among the Athabaskan Indians of Alaska (Mouratoff, 1969) and the Alaskan Eskimos (Mouratoff, 1967), diabetes is rare; however, some other native Americans have extremely high preva- lences. The Seneca and Cherokee Indians respectively, have been report- ed to have diabetes prevalence rates of 22% in those aged 25 and over (Doeblin et al., 1969), and 31% in those 35 years and over (Stein et al. 1965).

We have also determined the frequency of glucose intolerance in representative samples of many of the other southwest Indian tribes who except for the Papago, are unrelated to the Pima Indians (Table II) (Henry et al., 1969; Bartha et al., 1973).

Glucose intolerance in all of these tribes is greater than that generally believed to occur in other Americans, yet it is apparent that even within a restricted geographic area, highly significant differences in the prevalence of carbohydrate intolerance are encountered which are not satisfactorily explained on a genetic basis. For example, the Whiteriver and San Carlos Apache reside in adjacent areas of Arizona, although at substantially different elevations; from a genetic view- point, they are virtually indistinguishable, yet there is more than a two-fold difference between the two groups in their glucose intolerance rates. Such differences almost certainly point to environmental factor as major determinants of the differences in the prevalence of diabetes (Bennett, 1972).

The Pima Indians, however, have the dubious distinction of having the highest recorded prevalence of diabetes in the world. Since the community is relatively homogeneous, stable, geographically well-defined, and reasonable in size and accessibility for investigation, the Pima have provided an opportunity to examine the genetics and natural history of diabetes, as well as its complications. Consequently, most of our work has focused on extensive longitudinal investigations among the Pima.

The frequency distributions of glucose tolerance levels in most pop-
ulations have been reported to be unimodal with skewing towards higher
values, especially in older age groups (Butterfield, 1964; Hayner et al.,
1965). When similar distributions were plotted for the two-hour post-
load glucose levels in the Pima, the distributions were skewed and, in
the older age groups of both sexes, bimodal (Miller et al., 1968).

Use of the logrithmic values of the glucose levels stabilized the
variances and resulted in the normalization of the frequency distribu-
tions in the younger age groups. In each sex and in all decades aged
25 years and over, however, the distributions were bimodal and appeared
to conform to a model of overlapping Gaussian distributions. This fact
enabled the application of maximum likelihood methods to estimate the
parameters to describe the form of the distributions, and also provided
a means to test statistically the validity of the model, which proved
to be appropriate (Rushforth et al., 1971).

The bimodal frequency distributions and the component curves in the
Pima males and females are shown in Figure 1. The same model was also
found appropriate to describe the distribution of one-hour glucose
levels, although the degree of overlap of the two component distribu-
tions was greater (Rushforth et al., 1975).

The observation of bimodality has a number of important ramifica-
tions which make it a useful tool for examining several hypotheses.
The presence of two components in the distribution indicates that there
is biological heterogeneity of glucose tolerance in the Pima population,
resulting in a natural segregation into two subgroups, rather than the
hyperglycemic subjects constituting merely the upper end of continuous
distributions. This observation is consistent with the conventional
clinical concept of diabetes mellitus as a discrete clinical entity,
but the question of whether or not the subjects in the hyperglycemic
component of the distribution have or develop the specific manifesta-
tions of the disease remained. If so, then bimodality would provide a
logical mathematical basis for the determination of diagnostic criteria
which would enable the categorization of individuals by means other than
arbitrary criteria, and would allow a mathematical determination of the
degree of misclassification, not otherwise possible in the absence of an
independent marker for diabetes. This same property of the model also
facilitates comparison of the value of alternative blood sampling times
and has subsequently enabled quantitative assessment of the relative
value of the one-hour and two-hour post-load glucose determinations for
diagnosis (Rushforth et al., 1975).

The parameters of the bimodal frequency distributions, namely the means and variances of each component and the proportion of subjects falling in either the first or second component of the distribution, may be examined in relation to other characteristics such as sex, age, or obesity to determine whether these factors influence one or more of the parameters simultaneously. The parameters and properties of the bimodal frequency distributions of glucose tolerance offer new approaches to these problems and may also prove useful in determining the mode of inheritance of diabetes mellitus in the Pima (Steinberg et al., 1970a).

Having recognized the properties and possible significance of the bimodal glucose distribution, we re-examined the age-sex specific prevalence of glucose intolerance, using the best estimates of propor- tion of subjects falling in the hyperglycemic component of the glucose tolerance distributions of each sex and age group (Figure 2).

The frequency of hyperglycemia using this definition was still ex- tremely high, rising in the males from 2.5% at age 20 to 35.5% at 60 years of age, and in females to 49% at the same age. Beyond this age the prevalence was lower in both sexes (Rushforth et al., 1971). It is apparent that the excess in the prevalence of hyperglycemia in the females shown previously is much reduced and, in fact, the male to female difference in individual decades is no longer statistically significant. The main reason for the difference is that the mean of the lower compo- nent of the glucose distribution in the females was consistently higher than in the males and significantly so above 20 years of age so that, with the previously used single cut-off value of 160mg/100ml, a greater proportion of females whose glucose levels lay in the upper portion of the first component had been classified as "diabetic."

In both males and females, the mean of the first component increased somewhat with age, increasing between 20 and 70 years from 97mg/dl to 129mg/dl in the males, and from 104 to 151mg/dl in the females. This suggests that "normal" glucose tolerance does deteriorate somewhat with increasing age, and analysis of the mean glucose levels of the lower percentile levels of the glucose distribution in each age group tends to support this concept (Figure 3). Proof of the hypothesis, however, must await the results of long-term prospective studies.

As a high proportion of all subjects in the older age groups were tested, the fall in the prevalence of diabetes seen in the eighth decade is consistent with increased mortality in the diabetic population, since it is implicit that in these years the excess of mortality in the dia- betics had exceeded the incidence (rate of development of new cases).

Optimal cut-off values to minimize the misclassification of individ- uals as normal or abnormal have been determined for two-hour plasma glucose levels for each decade and each sex among the Pima Indians

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(Steinberg et al., 1970b). Such levels range from 204 to 227mg/dl in males and from 225 to 245mg/dl in the females, averaging 210 and 235mg/dl respectively. The proportion of individuals estimated to be classified erroneously by using these criteria averages about 5% -- an acceptable level for many purposes. These optimum cut-off levels are, however, 50 to 70 mg/dl higher than those frequently considered conventional criteria for the diagnosis of diabetes but are in general agreement with the upper limits of normality determined for Caucasians by Andres (Andres, 1970).

Diabetes is often associated with the presence of certain symptoms directly attributable to the carbohydrate intolerance; certain metabolic derangements that may sometimes lead to ketoacidosis; specific vascular complications, such as retinopathy and nephropathy; and excessive frequency of large blood vessel disease, leading to coronary heart disease and vascular disease in the lower extremities; and, in pregnancy, to complications which affect the outcome and the well-being of the infant.

To determine whether the hyperglycemic Pima subjects showed similar characteristics, and to determine whether or not the subjects in the two components of the glucose tolerance distributions corresponded to those with and without diabetes mellitus in the clinical sense, the occurrence of the more frequent complications and manifestations of diabetes was examined in relation to the duration and level of glucose intolerance.

The classical symptoms of polydipsia, polyuria, and weight loss are notoriously difficult to quantify. Nevertheless, the majority of the Pima with previously recognized diabetes had presented initially for medical care with these complaints, and, indeed, many of those with hyperglycemia documented for the first time also complained of polyuria. Since these symptoms are primarily related to the amount of glucose excreted in the urine, their frequent occurrence in the Pima is to be expected since glucosuria was usually present among the hyperglycemic subjects.

Ketoacidosis also occurs among the Pima with hyperglycemia, and in one instance was associated with death from mucromycosis (Miller et al., 1968). Since the frequency of ketoacidosis in non-Indian diabetics is unknown, it is difficult to judge whether this is a more or less frequent complication than elsewhere.

Glucagon and Insulin Levels

Glucagon levels in response to arginine infusion appear to be characteristic of subjects with diabetes mellitus. Figure 4 shows the effect of a 5mg/kg/minute infusion of arginine in Pima Indians with two-hour post oral carbohydrate plasma glucose levels of 230mg/dl and over and normal Pima controls. A significantly greater response was seen in the hyperglycemic subjects than in the controls, and fasting glucagon levels did not differ significantly in spite of considerable differences in fasting glucose levels between the groups (Aronoff et al., 1975a). These data indicate the similarity of Pima Indians with diabetes to

non-Indian diabetics insofar as they are characterized by having a relative fasting hyperglucagonemia and absolute hyperglucagonemia in response to an arginine infusion.

Insulin responses among Pima Indians show different patterns according to the level of glucose tolerance (Figure 5). Subjects who had two-hour plasma glucose levels of less than 120mg/dl after an oral carbohydrate load showed a rapid response within half an hour, rose slightly again at one hour, and fell subsequently at the two-hour point. Subjects with intermediate degrees of carbohydrate intolerance were similar within one hour of the glucose load, but then continued to rise at the two-hour sampling time. In contrast, subjects with higher glucose levels showed a sluggish response and failed to attain the levels seen at any sampling time in the other groups. Those with glucose levels of 400mg/dl and over, in fact, had no detectable response above the fasting level (Savage et al, 1975a). Those subjects who lie predominantly in the second mode of the glucose frequency distribution, therefore, have lower insulin responses than those in the first component of the distribution.

To determine whether there was any clear separation of the subgroups, the insulin levels at each sampling time were plotted against the corresponding two-hour glucose level as shown in Figure 6. The fasting levels showed no significant trend over a wide range of glucose tolerance. In contrast, the two-hour insulin levels increased in those with glucose levels of 80 to 170mg/100ml two hours after the carbohydrate load, and then, as glucose intolerance became more severe, a steady and consistent fall in mean serum insulin levels was seen. While it is clear that Pima Indians with severe degrees of glucose intolerance have an absolute hypoinsulinemia, those with intermediate tolerance levels and who would be found in the antimodal region of the glucose frequency distribution have circulating insulin levels considerably higher than those of the truly normal subjects, or those with severe diabetes.

These patterns do little to increase our understanding of the nature or mechanism of the bimodality of the glucose frequency distributions. They are, however, consistent with those reported in non-Indian subjects with similar degrees of glucose intolerance, and the complexity of the insulin glucose tolerance relationship is probably responsible for much of the controversy concerning the patterns of insulin response in diabetes.

Vascular Complications in the Pima Indians

The microvascular complications of diabetes are probably the most specific characteristics of the syndrome of diabetes mellitus. The two most frequent and clinically recognized are retinopathy and intracapillary glomerulosclerosis.

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Diabetic Retinopathy

Retinopathy has been assessed in the Pima Indians by means of ophthalmoscopy and, in addition, in those age 15 and over, by means of fundus photographs. Ophthalmoscopic evidence of retinopathy in either eye was determined following mydriasis without prior knowledge of the subject's diabetic status or glucose tolerance level. The presence or absence of each element of retinopathy, microaneurysms, hemorrhages, exudates, and proliferative and neovascular changes has been systematically recorded in a standard manner.

Microaneurysms or "dot" hemorrhages and exudates were the most frequently encountered abnormalities and both were significantly more prevalent than proliferative and neovascular changes, which were recorded in only 5-6% of those with retinopathy. The frequency of retinal changes increased in the total population with age in males up to age 60 and in females up to age 70 years. The frequency of retinopathy was not related to age, however, when the duration of known diabetes was taken into account. Some 50% of those with diabetes of ten years or more duration had retinopathy, compared to 18% in those with previously diagnosed diabetes of less than five years' duration (Table III) (Dorf et al., 1971).

The frequency of retinopathy in relation to the duration of diabetes in the Pima is similar to the trends reported from diabetes clinics (Caird et al., 1969), strongly supporting the premise that the retinopathy found in Pima Indian diabetics is essentially the same as that of non-Indian diabetics.

The frequency of retinopathy was also examined in relation to glucose tolerance level. Figure 7 shows the frequency distributions of the two-hour glucose levels in subjects aged 15 and over -- and, superimposed -- the frequency of subjects with one or more elements of retinopathy. The frequency of one or more retinal lesions was low among those who fell within the first component of the glucose frequency distribution and increased in the antimodal region, reaching a plateau in the body of the second component of the glucose distribution where the frequency of retinopathy ranged between 18-23%. Retinal lesions were found nine times more frequently in subjects with two-hour plasma glucost levels of greater than 200mg/100ml, compared to those with levels of less than 200mg/100ml. This observation provides strong support for the hypothesis that subjects falling into the hyperglycemic component of the glucose frequency distribution do indeed have diabetes mellitus and that the second mode, therefore, represents the true diabetic segment of the population. Retinopathy was recorded, however, in 25 subjects with two-hour plasma glucose levels of less than 200mg/100ml. Six of this group were previously diagnosed diabetics, four had hypertension, one a previous history of serious eye trauma, and nine had

only exudates. There were, therefore, only four males and females with microaneurysms or retinal hemorrhages (one of whom had exudates) for which there was no apparent explanation. These subjects may represent subjects with minimal degrees of diabetic retinopathy in the absence of glucose intolerance, but, in general, retinal lesions were encountered infrequently among those falling within the lower component of the glucose frequency distribution.

Renal Disease

The other frequent and specific microvascular complication of diabetes mellitus is intracapillary glomerulosclerosis. This diagnosis can be made only as a result of histologic evidence obtained by biopsy, or post mortem examination. Since renal biopsy is not feasible in a population study, indirect evidence of diabetic nephropathy was obtained by examination of the urine for proteinuria, and by serum creatinine determination. While these examinations are not specific, the demonstration of a greater prevalence of abnormal renal function among subjects with hyperglycemia would imply the presence of diabetic glomerulosclerosis.

Among those with previously diagnosed diabetes, the frequency of proteinuria increased with duration to 43% in those with history of glucose intolerance of ten years or more. Similarly, the proportion with an elevated serum creatinine level (equal or greater than 1.5mg/100ml) increased from 2.8% in those with diabetes of less than five years duration to 15% in those with ten or more years' duration. The frequency of severe proteinuria (urinary protein/creatinine ratio greater than 1.0) also increased from 9% to 31% in those with less than five and more than ten years' duration, respectively (Table IV).

Among the non-diabetics, however, 6.6% had some degree of proteinuria -- 0.9% level a P/C ratio equal to or greater than 1.0 -- and less than 0.5% had elevated serum creatinine levels. Thus, among the diabetics, proteinuria was 3.5 times as common, and severe proteinuria, 16 times as common in the diabetics as in the non-diabetics.

When the relationship between the level of glucose tolerance and frequency of proteinuria was examined, it was found that those with plasma glucose levels of over 200mg/dl had a frequency of proteinuria of 22.2%. Thus, evidence of renal dysfunction was found predominantly among those with previously diagnosed diabetes and with two-hour plasma glucose levels in excess of 200mg/100ml. This again confirmed that the hyperglycemic component of the glucose frequency distributions contained a much higher proportion with renal disease than the lower component, and that the frequency of renal disease was related to the duration of known carbohydrate intolerance (Kamenetzky et al., 1974).

While such information concerning renal function provides strong presumptive evidence of the presence of intracapillary glomerulosclerosis, only post mortem or biopsy data can provide specific information. The post mortem kidneys of 105 Pima Indians were examined systematically without knowledge of their previous diabetic status. The findings are summarized in Table V. Of the 32 who had had glucose intolerance, 65% showed moderate or severe diffuse glomerulosclerosis, 56% nodular glomerulosclerosis, and 44% exudative glomerular lesions. In contrast, evidence of nodular or exudative changes was not encountered in the non-diabetics and only two showed some evidence of a diffuse process. Arteriolar changes were also encountered much more frequently in the diabetic group. The post mortem data, therefore, indicate that the specific lesions of intracapillary glomerulosclerosis are encountered frequently and almost exclusively among Pima Indians who have had prior evidence of glucose intolerance during life. It is of interest to note that in only one instance was glomerulonephritis encountered and this in a non-diabetic subject.

Thus, a high prevalence of renal dysfunction and, in particular, the specific forms of intracapillary glomerulosclerosis thought to be pathognomonic of diabetes mellitus, occurred with high frequency among Pima Indians with diabetes, further strengthening the view that the manifestations and complications of hyperglycemia in the Pima Indians are identical to those seen in other races.

Muscle Capillary Basement Thickening

Further confirmation of the similarity of the histologic lesions associated with diabetes in the Pimas has been obtained by determination of muscle capillary basement membrane thickness in subjects without evidence of glucose intolerance, those with documented onset within the past five years, and those with a history of ten years' or more duration of hyperglycemia (Table VI). The specimens were obtained by needle biopsy from the quadriceps muscle, fixed in glutaraldehyde, and processed by Dr. Joseph Williamson. The mean minimum basement thickness of the normal subjects was significantly lower than that of the diabetics, and within the diabetic group, a highly significant difference was found between those of recent onset and long duration. These findings are similar to those in Caucasians with diabetes (Williamson et al., 1969).

Coronary Heart Disease

Evidence of coronary heart disease has been sought in standard twelve-lead electrocardiograms on all Pima Indians aged 15 years and over. In the population as a whole, definite electrocardiographic evidence of coronary heart disease among the Pima was less prevalent than in the general population of Tecumseh, Michigan, as shown in Figure 8. While no statistically significant differences in the frequency of

Q-wave, or ST and T wave changes were found between the diabetic and non-diabetic Pimas, the diabetics consistently, in each age group and each sex, had somewhat higher rates of electrocardiographic abnormality. In an attempt to verify the significance of this finding, we have examined the frequency of myocardial infarction encountered among 120 Pima Indians at post mortem examination. As shown in Figure 9, the frequency of myocardial infarction was rather greater in both male and female diabetics of corresponding age, but the difference between diabetic and non-diabetic subjects is again at this time statistically insignificant. These observations confirm earlier reports of the infrequency of coronary heart disease in the Pima and southwest Amerindians in general (Sievers, 1967).

The reasons for the low frequency of coronary heart disease among the Pima Indians and, in particular, among the diabetics are not known, but differences in the frequency of certain risk factors from those in non-Indian populations may possibly account for the low frequency in the Indian. Serum cholesterol levels in the Pima were low. In those aged 40 and over, they averaged 189mg/100ml in the non-diabetics, and 198mg/100ml in the diabetics -- levels considerably lower than in the U.S. population in general.

Even in the Pima population where diabetes mellitus is extraordinarily frequent, coronary heart disease was relatively unusual. The important implication of this observation is that coronary heart disease may not be an almost inevitable complication of diabetes mellitus. An understanding of the mechanisms whereby the Indian is protected from the development of coronary heart disease is of the utmost importance, since coronary disease is the leading cause of death among non-Indian diabetics in the United States and western Europe.

Mortality

Besides the toll of morbidity, the vascular complications of diabetes are primarily responsible for the shortened life expectancy of diabetics. In Caucasians, coronary heart disease accounts for more than half of the diabetic deaths; yet, since this complication is relatively infrequent among the Pima and evidence of myocardial infarction was present in fewer than 20% of the diabetics at the time of death, it was important to determine whether indeed diabetes was associated with a reduced life expectancy in the Pima.

The probability of death within an eight-year period beginning in 1965 has been determined in those who had diabetes or a two-hour plasma glucose level of 200mg/100ml and over at the baseline examination, and compared to that pertaining in non-diabetic subjects. Since the chance of dying is markedly related to age, the probability of death has been examined in the diabetics and non-diabetics according to age at the

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baseline examination. Figure 10 shows that the presence of diabetes had no particular measurable effect in those aged below 60 years, yet above this age the probability of death within an eight-year period in the diabetics was approximately 50% greater than in the non-diabetics. Renal failure was the primary cause of death in at least 20% of the diabetics, and an associated cause in many others. More meaningful interpretations of the force of mortality in the diabetics must await analysis according to the age of onset and the duration of the abnormality.

Diabetes and Pregnancy

Diabetes mellitus is well recognized as having characteristic effects on pregnancy and its outcome. To determine whether similar effects were found in the Pima Indians, a review was made of past pregnancies of females aged 25 to 44 years in January 1966, who had received a modified glucose tolerance test. On the basis of that test and the clinical history, the females were divided into those with two-hour glucose tolerance levels of less than 140mg/dl and those with plasma glucose levels of greater than 160mg/100ml. The latter group was further divided so that pregnancies occurring prior to the clinical diagnosis of glucose intolerance ("prediabetic") and those occurring after the diagnosis ("diabetic") could be separately analyzed. Based on 1253 pregnancies, the perinatal mortality rate in the normal and prediabetic pregnancies was 1.2% and 3.1% respectively, compared to a rate of 25.5% among the 47 diabetic pregnancies (Figure 11). The perinatal mortality was approximately equally divided between still births and neonatal deaths.

In all, 3.8% of the pregnancies were considered diabetic, which compares to a frequency in the population of Cleveland, Ohio, of 0.28%. Thus, the frequency of diabetic pregnancy was some ten to 15 times greater among the Pima Indians than among the women of Cleveland (Miller et al., 1968). The frequency of diabetic pregnancy in the Pimas was, therefore, in accordance with that which might have been predicted from the overall prevalence of hyperglycemia.

The diabetic pregnancies were also associated with an excessive frequency of heavy babies and congenital malformations among the infants. Some 43% of the diabetic pregnancies resulted in an infant weighing more than nine pounds at birth compared to 7% among the normoglycemia groups and 11% in the prediabetic group. The frequency of congenital anomalies among the infants was relatively high in all groups, averaging 3.8% in the normal and prediabetic pregnancies, but was significantly higher in the diabetics, where the rate was 19% (Comess et al., 1969). The higher frequency of congenital anomalies in the infants of diabetic mothers is consistent with previous reports (Pedersen et al., 1964). Among the diabetic mothers, there was, however, a small subpopulation of women characterized by an early age of onset of diabetes who were at

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particular risk of bearing anomalous children, suggesting that some particular metabolic abnormality may be primarily responsible for the excessive frequency of anomalous children. Some authors have also suggested that women predisposed to develop diabetes had a higher frequency of infants with anomalies. In the Pima, however, the prediabetic infant was at no greater risk than the infant of the normal mother. An ongoing prospective study is being made to attempt to determine more precisely the factors which influence the outcome of the diabetic pregnancy among the Pima.

The demonstration of significantly increased perinatal mortality, high infant birth weight, and a high frequency of congenital anomalies among these diabetic pregnancies further confirms that the hyperglycemia in the Pima Indians has the same pathologic significance as diabetes mellitus among Caucasians and Negroes.

Thus, the characteristics of hyperglycemic Pima Indians and the relationship of the complications to duration of known glucose intolerance conform closely to those seen in diabetics of other races. The specific microvascular complications such as retinopathy and intracapillary glomerulosclerosis occur frequently among those who have glucose tolerance levels which fall within the hyperglycemic component of the glucose tolerance frequency distribution, whereas they are rare or unknown among subjects whose glucose levels fall within the first component of this distribution. Except for coronary heart disease, the complications of diabetes appear to occur with approximately equal frequency in Pina Indian diabetics as in others with diabetes, and even in spite of the overall low prevalence of coronary heart disease, it appears that the diabetic Pima are at somewhat greater risk of developing this complication than are the non-diabetic tribesmen of similar sex and age.

It is reasonable, therefore, to assume that the major differences between the Pima Indians and other racial groups is that the Pima develop diabetes mellitus with much greater frequency than other races. The characteristics of the disease are similar, and therefore the major determinants of the disease itself and many of its associated complications are likely the same.

Etiologic factors in diabetes are presently ill-understood. Genetic determination is usually assumed to play an important role, and the frequency of obesity among some populations appears to correlate well with the prevalence of diabetes (West et al., 1971). Some authors have invoked the effects of child bearing as an explanation for the excessive frequency of diabetes among females (Pyke, 1956; Fitzgerald et al., 1961), although others have failed to find this association (Vinke et al., 1969; Jackson, 1961); and still others have invoked changes in specific components of the diet as important factors leading to the expression of diabetes (Yudkin, 1964; Cleave et al., 1969; Cohen, 1972).

Genetic Factors

Among the Pima Indians, diabetes shows unequivocal evidence of familial aggregation (Steinberg et al., 1971b). The proportion of offspring of diabetic parents with diabetes is considerably greater than among the offspring of normal parents. To the present time, however, the number of offspring whose parents have been categorized as diabetic or non-diabetic who have reached a sufficient age are too few to allow a meaningful genetic analysis to determine the mode of inheritance of the disease. We would also like to be able to determine rates of concordance in monozygous and dizygous twins to assess the relative importance of genetics and environment, but the population is not large enough to allow this approach. The importance of genetic determinants, however, is likely quite strong, as the rate of development of diabetes in the offspring of two diabetic parents is considerably greater than the rates of development of diabetes in the offspring of non-diabetic parents of similar age and weight. Over a six-year period, the incidence of diabetes was 9% in the "normal" offspring of diabetic parents, compared to 1.6% among the offspring of normal parents. These data, though, give no indication of the mode of inheritance and whether one or many genes are involved.

Parity

Because of the excess of female diabetics when either previous diabetes or a glucose tolerance criterion of equal or greater than 160mg/100ml two hours after the oral carbohydrate load was used, the relationship of parity to diabetes was examined among the Pima. Since the excess of diabetes in the females was confined to those aged 45 years and over as in the studies of Pyke and Fitzgerald and his associates (Pyke, 1956; Fitzgerald et al., 1961) and as many of the Pima women of this age had borne many children, the prevalence of diabetes according to the number of live born children was examined. Among 295 such women, no

relationship between parity and the prevalence of diabetes could be discerned. Similarly, in the younger women, the age specific prevalence of diabetes in those with 0, 1-3, 4-6, and 7 and more pregnancies was homogeneous, indicating that among the Pima parity has no effect on the rate of development of diabetes or that other factors overwhelm any possible effect of parity (Bennett et al., 1966).

Obesity

The degree of obesity encountered in the Pima Indians is striking. Among those aged 40 and over, the mean percent desirable weight averaged 122% in males and 149% in females. Thus, the majority of the population is obese according to Caucasian norms. It might be expected, therefore, that the prevalence of diabetes would show a strong and consistent relationship to the degree of obesity. Using conventional criteria for glucose tolerance, however, the prevalence of hyperglycemia beyond 45 years of age was not statistically different in those greater than 125% of desirable weight than in those of lesser weight. Nevertheless, up to the age of 35 years, the proportion of diabetics among the more obese was two to three times greater -- a difference which is statistically highly significant (Bennett et al., 1966). The different patterns of association with age suggest, therefore, that the degree of obesity perhaps influences the time at which diabetes appears rather than whether or not diabetes eventually develops. The lack of significant difference in the prevalence of diabetes in those aged over 45 implies that obesity per se is likely not the most important determinant of diabetes mellitus among the Pima, yet the striking association at younger ages suggests that obesity may be a precipitating factor which may cause the disease to appear at an earlier age than would otherwise have been the case.

The complex interrelationships between glucose tolerance and obesity were, therefore, examined using the parameters of the bimodal frequency distribution as a tool to enable better description of the nature of the association. As Figure 12 shows, the proportion of subjects falling in the diabetic component of the glucose frequency distribution was again no different in the older age groups, but was significantly different in the 25-34 year age group. The major effect of obesity on the form of the glucose distributions appeared to be that the mean of the first component of the glucose distributions is shifted to a higher level in the more obese subjects, whereas the proportions falling in the second component of the glucose tolerance distribution were substantially unaffected except in the younger decades (Rushforth et al., 1975b). Since the age-specific prevalence of diabetes was not consistently higher in the obese than in the non-obese and since prevalence of diabetes in the obese and non-obese over 45 years of age was not statistically different, it is clear that the high prevalence of diabetes among the Pima cannot be attributed simply to their degree of obesity. The prevalence data do suggest, however, that obesity may be a

precipitating or permissive factor, but proof of this hypothesis cannot be obtained from cross-sectional data, and requires the examination of incidence data.

Diet

The two most widely used foods in the Pima diet are beans and tortillas. The tortillas are prepared from wheat flour, rather than from corn, and these foods are eaten by most families at least once a day. Chili peppers are also consumed frequently, either eaten separately or included in stews or with beans. The diet of 79 diabetic women aged 25 to 44 years was compared and contrasted with that of 169 non-diabetics. Both groups had a high caloric intake, averaging 3160 calories per day. The percent of calories derived from protein, carbohydrate, and fat was comparable to that consumed by the general United States population, as was the ratio of saturated to polyunsaturated fats. The sucrose intake of the Pima was lower than that of the general United States population, averaging 64.3 ± 2.3 grams per day. Only minor differences were noted between the dietary intakes of the diabetics and non-diabetics. The diabetics reported that they ate almost 200 fewer calories per day and their sucrose intake was also statistically significantly lower than that of the non-diabetic, in spite of a mean percent desirable weight some 13% greater than that of the non-diabetics (Reid et al., 1971). It seems likely, however, that the lower sucrose intake was probably secondary to dietary instruction rather than being of any etiologic significance in the pathogenesis of their diabetes.

The extraordinary prevalence of diabetes mellitus among the Pima Indians provides a unique opportunity to determine the factors which lead to the appearance of glucose intolerance and its sequelae. If the appropriate characteristics in a sufficient number of subjects can be followed as they change from normal to diabetic, it seems likely that the sequence of events which leads to the development of glucose intolerance and later to the vascular complications could be documented. The goal of the prospective study in the Pima Indian is to do this, so that ultimately the mechanisms of decompensation of carbohydrate tolerance and vascular sequelae may be determined.

Cross-sectional and retrospective studies can only provide evidence of associations, but proof of cause is dependent on demonstration of the sequence of events in time. Thus, in the diabetic the simultaneous presence of hyperglycemia, obesity, hyperglucagonemia, and hypoinsulinemia yields a priori no information concerning the sequence in which these events have occurred. Furthermore, the demonstration that one of these events simply precedes the other is itself not adequate proof of cause and effect, since the two may be only indirectly related to each other. The appropriate temporal sequence, however, is a prerequisite to any consideration of a cause and effect relationship and represents a necessary step in the search of an underlying cause or mechanism.

If we are to study the circumstances leading to glucose intolerance, it is important to define the event as precisely as possible. Glucose tolerance is, however, notoriously variable, and a subject with a single level higher than an arbitrary threshold may remit on a subsequent determination. The fact that the frequency distributions of glucose tolerance in the Pima were bimodal gives some confidence that subjects within the second mode are probably unlikely to move into the first mode. This has, in fact, been shown to be the case (Ingelfinger et al., 1973).

Incidence of Glucose Intolerance

To determine suitable criteria for the recognition of recently developed glucose intolerance, the glucose tolerance level (logarithmic values) of subjects aged 15 to 74 at the first and subsequent examinations two to four years later were compared in those whose glucose tolerance fell into the normal component of the frequency distribution at the first examination. It was found that simple linear regression equations could predict the average changes occurring in each sex and decade. These regression equations were then used to predict the individual retest glucose tolerance values from those at baseline. The

predicted and observed retest values were then compared to determine the degree and variability of the differences.

The differences between predicted and observed retest values also had a bimodal frequency distribution, with the majority of the population falling around zero, suggesting the adequacy of the regression model, and a smaller subgroup characterized by positive differences, which were clearly beyond the expected range. Thus, subjects with glucose tolerance which had deteriorated to an unusual degree over a four-year period were identified. It was possible to characterize these subjects in terms of age and sex, earlier glucose tolerance, and other characteristics such as weight.

Age-Sex Specific Incidence of Diabetes

The age-sex specific incidence of diabetes is shown in Figure 13. The rate of development peaked at 35 to 44 years and was low below the age of 25 years and over 55 years. The relative frequency in the males and females was similar.

To verify whether or not the estimates were reasonable, the cumulative incidence was compared to the previously described prevalence estimates (Figure 14). The correspondence between the two estimates is good up to the age of 55 years, after which the prevalence rates fall below the cumulative incidence rates due to the excessive mortality of diabetics.

The significance of these findings is that glucose tolerance tests tend to deteriorate markedly over a short time period (e.g., up to four years) in the majority of Pima who develop diabetes, rather than changing insidiously over a much greater time period. The relative rapidity of change had been previously inferred from the baseline glucose tolerance distributions (Rushforth et al., 1971), since, if large numbers of subjects were gradually decompensating, the separation of the two distributions would have been obscured by the presence of many persons with intermediate glucose levels.

Glucose, Obesity and Diabetes Incidence

The incidence of diabetes defined in this way was also found to be related to the degree of obesity, the previous glucose tolerance level, and family history of diabetes (Ingelfinger et al., 1973), as had been previously suggested on the basis of the 17-year follow-up of the Oxford Diabetes Study (O'Sullivan et al, 1965; O'Sullivan, 1969).

These conclusions have now been substantiated in the Pima using an alternative definition of diabetes and a life table method to calculate the incidence. Using this approach over an eight-year period, the peak incidence was confirmed to lie between 25-44 years of age and was

related to obesity and previous glucose tolerance (Hamman et al., 1975). Table VII shows that the risk of diabetes over the eight-year period was 5% in those weighing less than 125% desirable weight with two-hour plasma glucose levels less than 160mg/dl, compared to a rate of 75% among those who were over 150% of desirable weight with two-hour glucose levels between 160 to 199mg/dl at the baseline examination. Both obesity and glucose level were statistically significant independent risk factors, but when both obesity and high glucose levels occurred together, they acted synergistically producing a 15-fold greater risk than when weight and glucose levels were both normal.

Obesity and Glucose Levels Prior to Onset of Diabetes

Since obesity has been implicated as an important risk factor and as obese Pima Indians have been shown to have higher insulin levels than the less obese (Savage et al., 1975a), we have examined the characteristics of insulin secretion in genetic prediabetic Pimas and normal Indians (subjects with normal glucose tolerance whose parents also both have normal tolerance). (Aronoff et al., 1975b).

Figure 15 shows the insulin responses to rapid (three minute) 25 gm intravenous glucose infusions in these groups. In both normal and prediabetic subjects the peak response was seen five minutes after starting the infusion and no significant differences in the early phases of the insulin response were apparent, although minor differences were seen in the late phases, e.g., 60 minutes after infusion.

The insulin responses to an oral carbohydrate load were also determined on 14 subjects who subsequently developed overt glucose intolerance (two-hour glucose greater than 275mg/dl) at a time when their two-hour glucose levels were less than 160mg/dl. These subjects were compared to matched controls, who had initially similar glucose levels and weight, but whose glucose tolerance remained normal over the subsequent four years (Savage et al., 1975b). No differences in insulin levels either fasting or over the two-hour test period were demonstrable. Thus, both in genetic and "true" prediabetic subjects, compared to normal Indians, significant differences in early insulin response were not demonstrable. This conclusion contradicts the hypothesis of diminished early insulin response as a prediabetic characteristic (Cerasi et al., 1970).

Glucagon Levels in Prediabetic Pima Indians

Further evidence that altered insulin secretion may not be the precipitating cause of glucose intolerance in the Pima Indian was obtained by examining the insulin and glucagon responses to arginine infusion of the Pima diabetics. Figure 16 shows glucagon responses in recent onset

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diabetics never severe enough to require insulin treatment, whose circulating insulin levels were higher than in normal controls, but who, in spite of the hyperinsulinemia, had significantly elevated glucagon responses. The responses in these diabetics were similar to those of other diabetics, who were more severe and had received insulin treatment, but who had lower circulating insulin levels than normal controls. Thus, these data provide evidence that the hyperglucagonemia of diabetes is independent of the circulating insulin level (Aronoff et al., 1975a). They also indicate that hyperglucagonemia is present at a stage in the course of diabetes when insulin levels are not diminished, yet where the presence of glucose intolerance is unquestionable.

These findings provide some support of the hypothesis that hyperglucagonemia is an essential and possibly a primary lesion leading to hyperglycemia in the diabetic, as has been suggested by Unger and his associates (Unger et al., 1972; Unger et al., 1975). We have, therefore, examined the glucagon response to arginine in genetic prediabetic Pima Indians to determine if hyperglucagonemia might even precede decompensation, but no differences could be found in the glucagon responses in this group compared to either normal Pima Indians or Caucasian controls (Aronoff et al., 1975c).

Insulin Levels in Pima Indians and Caucasians

During the studies of the prediabetic and normal Pima Indians, insulin levels in response to oral carbohydrate and to rapid intravenous glucose infusion were also compared to those of Caucasians of similar age.

A major difference between the Indians and Caucasians in the magnitude of the insulin response to both stimuli was found (Aronoff et al., 1975b). In response to intravenous glucose, both Pima Indian groups had approximately a two-and-a-half-fold greater response than the Caucasians. This difference was not attributable to differences in the degree of obesity, since the magnitude and the statistical significance of the differences persisted after correction for this variable (Figure 17). No specific reasons for this apparent racial difference are known, although the possibility of such difference has been suggested previously (Rimoin, 1969).

In view of the close relationship of insulin to the regulation of carbohydrate metabolism, and, although a change in insulin secretion does not always appear with decompensation of glucose tolerance, it is tempting to speculate that this abnormality may bear some relationship to the propensity of the Pima Indians to develop diabetes, especially as hyperinsulinemia is associated with the presence of obesity, which, in turn, is an extremely important risk factor for the development of diabetes. Is it possible that the hyperinsulinemia is the cause of the

obesity, which is also so prevalent among the Pima, or is the hyperinsulinemia a secondary to obesity or compensatory response to an inherited insulin receptor defect?

Hypothesis

The presence of hyperinsulinemia at a time when glucose tolerance is normal in subjects from a population characterized by a high prevalence of diabetes is consistent with the hypothesis of diabetes as a "thrifty genotype" rendered detrimental by progress, which has been proposed by Neel (Neel, 1962). Neel suggested that subjects from populations which had been subjected to fluctuations of food supplies and who might have experienced periods of abundance alternating with periods of famine, might have developed a propensity to store foods as adipose tissue in times of abundance, and at the same time maintain normal blood sugar levels. This trait he believed could offer selective advantages for survival during a period of famine and, therefore, could have become very common in the population through the mechanism of genetic selection.

Neel postulated that gene selection for "hyperinsulinemia" would occur if these conditions were present for many centuries, provided that the selective advantages outweighed the disadvantages. The advantages of the propensity to store energy as fat in times of abundant food supply would likely outweigh any disadvantages, until such time as food supply became constant and abundant. At this time, obesity would supervene and its consequences or complications -- for example, diabetes mellitus -- would become manifest and appear more frequently than in populations where the forces for genetic selection to lay down energy stores were less strong.

Such variation in food supply has certainly occurred among the desert dwelling Indians, particularly those primarily dependent on agriculture for much of their food, such as the Pima and Papago Indians, since cyclic variations in rainfall over periods of years, as reflected by tree ring studies, are a natural and normal component of their desert environment (Haury, 1967).

The hypothesis also suggests similarities between the Pima Indians and many of the animal models for diabetes. Such animals, many of which reside normally in a desert environment -- e.g., Egyptian sand rat, Chinese hamster, Tuco-Tuco -- when fed a constant standard laboratory diet, become obese and hyperinsulinemic, and develop hyperglycemia (Renold et al., 1970). Whether the mechanisms that produce hyperinsulinemia, obesity, and hyperglycemia in the animal models are similar to those operating in the Pima Indian is not yet known.

Many questions remain unanswered, but it seems quite probable that the Pima Indians will help unravel these mysteries and ultimately those of the pathogenesis of diabetes in man.

Epidemiologic methods may be used to further enhance our understanding of mechanisms which may underlie the rate of development or rate of progression of the microvascular complications in diabetic subjects. As shown earlier, the specific microangiopathic complications of diabetes are strongly related to the duration of known glucose intolerance, yet the evidence that these complications are a function of the plasma glucose level within the diabetic subpopulation is lacking. Furthermore, the available prospective trials of the effects of hypoglycemic therapy on the rate of development of the microvascular complications have failed to show any difference compared to placebo treated subjects (University Group Diabetes Program, 1971). We have, therefore, examined the relationship of retinopathy and renal disease in the Pima Indians to other variables.

Both retinopathy and proteinuria showed unexpectedly strong relationships with blood pressure. Among diabetics with normal blood pressure, the prevalence of retinopathy was 6% compared to 32% in subjects with systolic blood pressures equal to or greater than 160 mmHg (Table VIII). Proteinuria showed a similar relationship to blood pressure. Since blood pressure might also be a function of duration of diabetes, the frequency of both retinopathy and proteinuria then were examined in relation to blood pressure level, stratified for duration of known diabetes. Evidence of strong and statistically significant relationships between the frequency of retinopathy and both systolic and diastolic blood pressure remained after correction for differences in duration of known diabetes (Kamenetzky, 1973). Since hypertension may also be a complication of diabetic nephropathy, the frequency of retinopathy in persons without any clinical evidence of nephropathy was examined. Even after taking into account the duration of diabetes, significant difference remained between the frequency of retinopathy within the hypertensive group compared to the normotensive group. The fact that hypertensive retinopathy was not contributing significantly to this relationship was ascertained by examining the relative frequency of retinal lesions in the non-diabetic group; only a small percentage of hypertensive subjects had retinal lesions. These data led us to suspect that the rate of development of retinopathy within diabetics might be dependent upon the blood pressure.

Since it was possible that the retinal lesions and the hypertension had developed concomitantly in the same subjects and both were manifestations of the same underlying process, the incidence of retinopathy among newly recognized diabetics, classified according to baseline blood pressure levels at the time of diagnosis, was then determined. Table IX

shows that a relationship was found between the rate of development of evidence of microaneurysms and the baseline blood pressure within this group. Subjects with baseline systolic blood pressures of less than 140mmHg were subdivided into those who remained normal and those who developed some evidence of hypertension prior to the appearance of microaneurysms. In subjects with newly recognized diabetes who had blood pressures under 139mm in mercury, 8% developed microaneurysms compared to 32% in those whose blood pressures had exceeded this level.

It appears, therefore, that blood pressure may play an important role in the rate of development of the microangiopathy of diabetes. Since both retinal and renal lesions occur together much more frequently than would be expected by chance, and probably have a similar etiology, it seems possible that careful control of blood pressure within the diabetic may delay the onset or slow the progression of both of these complications. This hypothesis could be tested by means of a controlled clinical trial and, if correct, could lead to the prevention or slowing of the course of microvascular disease in the diabetic.

The epidemiologic studies of diabetes conducted in the Pima so far have considerably enhanced our knowledge of the distribution and determinants of diabetes and its specific complications. This has been possible because a sufficient number of diabetics were found in the population and the incidence of diabetes within the population was relatively high. In addition to cross-sectional studies, prospective studies whereby incidence data, rather than prevalence data, can be collected have been possible. The prospective phase provides means by which hypotheses concerning etiology and pathogenesis can be developed much more effectively than when only cross-sectional or prevalence data are available. The epidemiologic studies have also defined important areas for investigation by alternative methods. We believe that the studies carried out so far among the Pima Indians offer a number of important clues relating to the pathogenesis of diabetes which are susceptible to more intensive investigation by the methods of clinical, epidemiological, and laboratory research. If successful, these studies will lead to a better understanding of the pathogenetic mechanisms underlying diabetes mellitus and its complications which will have general applicability.

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TABLE I

TWO-HOUR POST-LOAD GLUCOSE LEVELS AND PREVALENCE OF DIABETES IN HALF TO FULL BLOODED PIMA INDIANS

AGE GROUP (Years)	Number Examined	Two Hour Venous Plasma Glucose (mg/100 ml)							With diabetes			
		0-99	100-139	140-159	160-199	200-299	300-399	400&over	Previously Recognized No.	%	≥160mg/100ml* No.	%
MALES												
5 - 14	547	280	249	16	2	-	-	-	0	0.0	2	0.4
15 - 24	239	121	95	15	3	2	1	2	1	0.4	8	3.4
25 - 34	135	39	58(1)	8	8	8	3	10	8	5.9	30	22.2
35 - 44	142	39(1)	44(1)	8	6	8	15	20	26	18.3	51	35.9
45 - 54	94	12	35	8	7	8	12	12	21	22.3	39	41.5
55 - 64	84	16	25	8(1)	4(1)	7	11	11	23	27.4	35	41.7
65 - 74	76	9(1)	20(1)	11	9	7	7	11	21	27.6	36	47.4
75+	41	4	13	6	5(1)	6	3	3	7	17.1	18	43.9
TOTAL	1358								107	7.9	219	16.1
35 & over	437								98	22.4	179	41.0
FEMALES												
5 - 14	604	272	293	24	13	2	-	-	0	0.0	15	2.5
15 - 24	307	131	143	18	9	2	1	3	3	1.0	15	4.9
25 - 34	187	39	87	20	15	12	5	9	11	5.9	41	21.9
35 - 44	178	11	64(1)	14	26(3)	17	21	21	41	23.0	89	50.0
45 - 54	107	9	26	5(2)	12(2)	17	8	26	40	37.4	67	62.6
55 - 64	102	4	16(1)	12(1)	4(4)	15	18	27	54	52.9	70	68.6
65 - 74	59	1	15	8	6	13	9	7	21	35.6	35	59.3
75+	15	2	6	-	-	5	2	-	2	13.3	7	46.7
TOTAL	1559								172	11.0	339	21.7
35 & over	461								158	34.3	268	58.1
BOTH SEXES												
TOTALS	2917								279	9.6	553	19.1
35 & over	898								256	28.5	447	49.8

*Includes subjects, shown in main table in parentheses, who had diabetes clearly confirmed by medical record review and who were mostly taking hypoglycemic agents, but in whom the two-hour plasma level was lower than 160 mg per 100 ml.

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TABLE II

PREVALENCE OF CARBOHYDRATE INTOLERANCE AMONG NATIVE AMERICANS AGED 35 AND OVER IN THE UNITED STATES

Tribe	Number Examined	Percent with Diabetes[a][b]
Apache, White River	268	11.0
Apache, San Carlos	317	24.8
Navajo	55	12.8
Washoe	66	16.9
Paiute	54	25.9
Upland Yumans	313	29.9
Zuni[c]	292	31.3
Cocopah	79	33.3
Papago	365	42.3
Pima	898	49.6

[a]Mean of male and female rates

[b]Plasma glucose concentration $\geq$160mg/100ml two hours after a 75 gm carbohydrate load

[c]Plasma glucose concentration $\geq$180mg/100ml one hour following a 75 gm carbohydrate load

TABLE III

PREVALENCE OF RETINOPATHY IN RELATION TO
DURATION OF DIABETES IN PIMA INDIANS AGED 15 AND OVER

		Duration of Diabetes (years)		
	Newly Diagnosed	<5	5-9	10+
No. of subjects	128	134	76	62
Percent with Retinopathy	3.1	17.9	19.7	46.8

TABLE IV

RENAL DISEASE IN PIMA INDIANS AGED 15 AND OVER
WITH DIABETES

Percent of Subjects

Duration of Diabetes (years)	No. of Subjects	Proteinuria >30mg/dl	Protein/Creatinine>1.0	Serum Creatinine >1.5mg/dl
0 - 4	143	14.6	9.1	2.8
5 - 9	81	25.0	18.5	6.2
>10	65	43.1	30.8	15.4
TOTAL	289	23.2	16.6	6.6

TABLE V

DIABETIC NEPHROPATHY IN THE PIMA INDIANS

Summary of autopsy data

		Diabetic	Non-diabetic	Significance (p)
Number examined	105	43	62	
Males	61	25	36	
Females	44	18	26	
Mean Age (yrs.)		62.3	59.3	
Percent with:				
Moderate or severe diffuse glomerulosclerosis		65.1	3.3	0.001
Nodular glomerulosclerosis		55.8	0.0	0.001
Exudative glomerular lesions		44.1	0.0	0.001
Arteriolar changes		76.7	14.5	0.001
Pyelonephritis		16.3	5.0	N.S.
Glomerulonephritis		0.0	1.7	N.S.

TABLE VI

CAPILLARY BASEMENT MEMBRANE THICKNESS
IN PIMA INDIANS

	NORMAL	DIABETICS	
Duration		0-5 years	>10 years
B.M.T. ($\overset{o}{A}$) ($\overline{X}$ ± SEM)	890±40	1369±127	2165±162
No. of Subjects	25	12	21
Significance		p=0.001	p<0.001

(Williamson method)

TABLE VII

EIGHT-YEAR INCIDENCE OF DIABETES (PERCENT ±2 SEM) IN PIMA INDIANS AGED 15 AND OVER ACCORDING TO INITIAL TWO-HOUR PLASMA GLUCOSE LEVELS AND PERCENT DESIRABLE WEIGHT

Baseline Characteristics Glucose Level (mg/dl)		Initial Weight (% desirable)		
		<125	125-150	>150
<160		5 ± 3.3^{A}	17 ± 6.8	32 ± 9.3
	N	474	308	247
160-199		29 ± 23.7	40 ± 28.4	75 ± 17.8
	N	23	24	42
Risk		1.0	3.4*	6.4**
Ratios		5.8*	8.0**	15.0***

^{A} 2 standard errors

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

TABLE VIII

FREQUENCY OF RETINOPATHY ACCORDING TO DURATION OF
DIABETES AND SYSTOLIC BLOOD PRESSURE IN PIMA INDIAN DIABETICS

Systolic Blood Pressure(mmHg)	Newly Diagnosed	Duration (years)		
		<5	5-9	10+
<140	0/58 (0)	3/64 (5)	2/28 (7)	5/17(29)
140-159	2/31(6.5)	8/38(21)	5/23(22)	8/20(40)
160+	2/39(5.1)	13/32(41)	8/25(32)	16/25(64)

( ) Percent with Retinopathy

TABLE IX

INCIDENCE OF MICROANEURYSMS OVER A 4 YEAR PERIOD
IN DIABETICS INITIALLY WITHOUT RETINAL LESIONS
BY BASELINE BLOOD PRESSURE

Blood Pressure (mmHg)		No. of	Incidence of
Baseline	Subsequent	Subjects	Retinopathy (%)
<140	<140	49	8
<140	≥140	31	29
140-159		38	34
160+		27	33

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IV. Report of the

WORKGROUP ON

MORTALITY

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

George K. Tokuhata, D.P.H., Ph.D.

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IV.   REPORT OF THE WORKGROUP ON MORTALITY

A.   STATEMENT OF THE PROBLEMS

Despite serious complications, premature deaths, and profound
socioeconomic implications, diabetes mellitus -- its nature and
magnitude -- has not received sufficient recognition as one of the
most significant public health problems in the U.S. today.

Probably the most important reason for this lack of recognition
is that certain technical problems get in the way of how diseases
are classified, problems which affect particularly the selection of
diabetes as a cause of death. Under the existing mortality report-
ing system, only one disease is counted as the underlying cause of
death, even when several other often-related diseases are diagnosed
in the same patient. Diabetes may be recorded on the death certifi-
cate as a contributory cause, but not officially reported out. Fur-
thermore, diagnosed diabetes is not even recorded on death certifi-
cates in approximately 10% of deaths. Another significant reason
for the inadequate reporting is the very definition and nature of
diabetes itself as an insidious chronic disease. For these reasons,
physicians tend not to choose diabetes as the underlying cause in
the presence of more "visible" diseases, many of which may, in fact,
have been caused either directly or indirectly by diabetes.

At the turn of the century, diabetes ranked 27th as a cause of
death by disease. Since then, diabetes has increased steadily as a
cause of death until it now ranks as the fifth leading underlying
cause by disease (sixth by all causes) as reported in the U.S.
However, this ranking position given to diabetes among major causes
of death is misleading, for, under the existing mortality reporting
system, a large number of people with diabetes who die from its
complications are usually not counted as having died of diabetes.
Whether diabetes is the underlying cause of death or a contributory
cause, it is possible that diabetes should be considered the third
leading cause of death in the United States.

The term "diabetic complications," when used in the context of
mortality, is poorly defined and has been used indiscriminately.
This state of confusion is due primarily to the difficulty in deter-
mining which of the significant pathological conditions often associ-
ated with diabetes are actually "caused" by diabetes.

"Diabetic complications" that may lead to death can vary accord-
ing to the type of diabetes affecting the individual patient, i.e.,
juvenile-onset diabetes as compared with adult-onset diabetes. Since

age at first diagnosis of diabetes is not usually recorded on death certificates, death certificates do not provide any useful means for providing such information at present.

There is also a problem of misallocation of place of residence on the death certificate. Not necessarily limited to diabetes, this issue is important because death certificates provide data on residence by civil divisions and municipalities, and have been widely used to assess disease problems by geographic location.

B. IMPACT OF THE PROBLEMS

Since diabetes is not always selected as the underlying cause of death when it is mentioned on death certificates, and since diabetes is often not even recorded on death certificates when it is diagnosed at the time of death, its prevalence is grossly underestimated according to traditional mortality statistics. Furthermore, the specific nature and magnitude of "diabetic complications" in relation to life expectancy have not been fully documented. This poor visibility and lack of understanding, in turn, lead to an underestimation of the complex health problems diabetes poses. Consequently, medical research and social programs related to diabetes have not been funded at a level commensurate with its importance as a major disabling condition and a significant cause of death. Since the advent of insulin, there have been no major medical breakthroughs either in the primary (keeping from incidence) or secondary (arrest of progression) prevention of this disease.

Diabetes is a common chronic disease affecting all ages (including the perinatal period) -- with the juvenile-onset (insulin-dependent) type far more serious in its medical complications than the adult-onset type. Thus the potential benefit of an effective diabetes control program would be much greater than that of other chronic disease programs in which only adult populations may be affected.

C. STATE OF THE ART

1. INTRODUCTION

The problems associated with diabetes mortality are multidimensional and interrelated. Since mortality statistics are essentially based on data from certificates which are prepared, in part, by physicians, these problems often originate with the physician's imperfect knowledge of his patient's medical history and an inadequate

understanding of the rules of death certification, particularly with respect to selecting diabetes as either underlying or contributory cause of death.

Subsequent problems are those of analyzing, interpreting, and reporting diabetes -- obscured by its many complications and other competing risks -- in official mortality statistics. Problems in diabetes mortality also occur in distinguishing the juvenile-onset type from the adult-onset type on death certificates and in determining the true difference between urban and rural areas because of a rather systematic bias (to be discussed below) in the allocation of the place of residence as recorded on death certificates.

In view of the nature of the problems described above, the State of the Art will be presented in the following separate but related sections: (2) Diabetic Complications; (3) Death Registration; (4) Diabetes Mortality: Underlying Cause of Death; (5) Diabetes Mortality: Multiple Cause of Death; (6) Life Expectancy and Survival Among Diabetics; (7) Statistical Models.

2.   DIABETIC COMPLICATIONS

The full impact of mortality resulting from diabetes is difficult, if not impossible, to measure. Diabetic complications in relation to mortality are important -- for instance, the causal relationship between diabetes and vascular disease, particularly large vessel disease, which has not been fully delineated. In a significant number of instances, diabetes is not recorded as the underlying cause of death when the immediate cause of death is vascular disease. Many of the microangiopathies related to diabetes are probably better understood, but much less likely to be recorded as a cause of death.

Numerous studies have shown that vascular disease is the predominant cause of death among diabetics. In younger diabetics, the vascular disease is manifested primarily as microangiopathy, and in older diabetics as macroangiopathy.

An analysis of deaths among patients at the Joslin Clinic (23) has shown that 76% of the deaths were due to vascular disease of all types. Fifty-one percent of the deaths were due to cardiac disease and approximately 30% due to coronary artery disease. Renal-vascular deaths occurred in 9% of the patients and cerebrovascular deaths in almost 13%. In comparison with the general population, total vascular disease among diabetics resulted in 2.4 times the number of deaths among males and 3.4 among females. Heart disease was two times more common as a cause of death in diabetic males and 3.2 times

in diabetic females. The respective figures for cerebrovascular
disease were 1.8 for males and two for females, and, for renal-
vascular disease, 17.8 for males and 17 for females. The marked
excess in deaths for renal-vascular disease occurred at the younger
ages, with heart disease the predominant cause of death at the middle
and older ages. After age 60, the frequency of deaths from heart
disease declined, with a corresponding increase in deaths from
cerebrovascular disease.

A postmortem study of diabetics done in 1952 by Bell (5) listed
vascular disease as the major and leading cause of death on 50.7%
of 1,555 necropsies. Of the vascular diseases, coronary artery
disease accounted for 18.5%, peripheral atherosclerosis for 12.7%,
and cerebrovascular disease for 7.7%. In a control group of 4,419
apparent nondiabetic patients, vascular disease was judged respon-
sible for only 24.5% of deaths.

Studies of the causes of death among insured diabetics have also
shown the excessive number of deaths due to cardiovascular disease.
A recent study (27) showed that at ages 20-39, 29% of the deaths
were due to coronary artery disease compared to 10% in the general
population. At ages 40-69, the percentage of deaths from coronary
artery disease among diabetics varied from 12% to 28%. These
studies, along with others, have demonstrated an earlier occurrence
of coronary artery disease and also a high female mortality from it.

As mentioned previously, the mortality from cerebrovascular
disease increases with advancing age. Although there is an excess
of cerebrovascular deaths at the younger adult ages, it is not nearly
as marked as for coronary artery disease. Whether the relationship
between diabetes and cerebrovascular disease is as direct as that
for coronary artery disease remains unsettled. It seems reasonable
to assume, however, that diabetes is a causative factor for ather-
osclerotic disease regardless of which blood vessels are affected.
In the past several decades, peripheral vascular disease has not been
significant as a cause of death among diabetics. Fewer than 2%
of deaths among diabetics are listed as being caused by either
peripheral vascular disease or gangrene.

In recent years, studies (83, 4) have determined that the preva-
lence of hyperglycemia is increased in populations with atherosclerotic
vascular disease. Most of these studies have been done among patients
with coronary artery disease, but a similar increased prevalence has
been noted for other forms of severe atherosclerosis. The studies
of patients who have had myocardial infarctions have shown varying
results because of lack of satisfactory control data and lack of
uniformity in the time interval that the glucose testing was done
after the acute myocardial infarction. The consensus remains,

however, that there is an increased frequency of hyperglycemia in patients who have had myocardial infarctions. If it is established that hyperglycemia plays an etiologic role in the development of atherosclerotic disease, then the importance of diabetes is further increased.

Analysis of the Joslin Clinic experience (9) of 2,634 deaths among diabetic patients from 1960 to 1964 revealed that 78% were due to cardiovascular-renal diseases. Coronary heart disease accounted for 53% of all deaths during this period.

In an autopsy study of 50,775 subjects, published in 1949 (11), there were 1,182 persons with diabetes. Fatal coronary heart disease was almost twice as frequent in diabetic males as in nondiabetic males, and three times as frequent in diabetic females as in non-diabetic females. Among diabetic patients, the frequency of fatal coronary disease was almost as high in women as in men. These differences are due, to a significant extent, to differences in the age composition between diabetics (older) and nondiabetics (younger) and between women (older) and men (younger).

Thomas and associates (78) studied 500 patients who died from acute myocardial infarction -- reporting the results in 1956. They found that the incidence of myocardial infarction was four to ten times greater among diabetics than nondiabetics, and that the proportion of those diabetic persons who died from acute heart disease increased by almost two times for males and by nearly four times for females. These differences, however, were to a significant extent also due to differences in the age factor. From data such as this, it is impossible to determine to what extent diabetes was actually responsible for an increased risk of heart disease.

A long-term autopsy study reported in 1959 by Goldberg and associates (91) indicated that hypertension and myocardial infarction were about twice as frequent in diabetic as in nondiabetic patients. Again, the age factor was not taken into consideration in this analysis.

The prospective experience of 258 patients admitted to the New England Deaconess Hospital in Boston (56) provided some interesting differences in mortality patterns with respect to diabetes. The results showed that the longer the duration of diabetes, the poorer the prognosis for both immediate death from acute myocardial infarction and five-year survival. The authors concluded that age, duration of diabetes, and diabetic nephropathy were of great importance for both immediate mortality and five-year survival. It should be noted that age and duration of diabetes are closely related to each

other, and that the age factor must be held constant when the duration factor is evaluated.

3. DEATH REGISTRATION

  a. The System:

       The death registration system in the United States is part of the complex, decentralized, cooperative vital statistics registration system, the control of which is vested in the individual states and certain independent registration cities. Untold numbers of persons -- physicians, funeral directors, hospital personnel, nurses, medical record librarians, clerks, government employees, etc. -- are responsible for maintaining the system. Uniformity is obtained by a periodic issuance of recommended standards from the National Center for Health Statistics, and their cooperative adoption by the states. The real quality of the system and the vital statistics obtained through it, however, are dependent on the conscientious efforts of a large number of individuals.

       The death certificate in the United States is completed jointly by physicians and funeral directors. It is then for-warded to local registrars, who provide burial permits, and then to the state registrar. Certificates are permanently filed in the states, and copies are sent to the National Center for Health Statistics (NCHS) for their use in preparing national data. A detailed description of the flow of the certificate is provided in the Appendix.

       Under such a system, considerable variation among the states is to be expected. For this workgroup report, it was not possible to conduct a survey of the states to determine death registration practices because of time constraints, but it is a fair assumption that practices vary considerably.

       What effect these presumed differences have on the quality of the data reported is not known. Each state modifies the Standard Certificate of Death according to its particular needs, or by special provisions of state vital statistics laws. NCHS, however, indicates that the certificates of many states con-form closely in content and arrangement to the Standard Certificates. Mountin and Flook in a 1943 analysis of State Health Department organization found variations among the states with respect to both the establishment of registration districts and the method of appointing local registrars (51). An earlier study (in 1939) of the effectiveness of different

systems of collecting vital statistics data showed that the routing of reports of births and deaths is subject to much variation (17). While current data on individual state registration systems are not available for evaluation, NCHS does provide a general description of how the vital statistics registration system in the United States operates (see Appendix).

b. Medical Certification of Cause of Death:

The medical portion of a death certificate is designed to obtain information on the underlying cause of death and on the causal and pathological sequence of events leading to death. Thus, the physician certifying the cause of death also completes items relating to hour, date, and place of death; the period during which physician attended the deceased; autopsy; and accident and injury.

The most important among these is information on the cause of death, since, in addition to its legal uses, it is also widely used in health research. However, the problem of obtaining proper medical certification of causes of death is a difficult one, and the quality of reported diagnostic information is frequently questioned. Part of the problem is that death is frequently due to a complex of diseases and the underlying cause cannot be readily delineated. Other problems are due to inadequate information about the circumstances of death, especially in the event of sudden death. Furthermore, physicians receive little formal, systematic instruction in medical schools or hospitals concerning medical certification of causes of death. In most instances, a physician completes a death certificate for the first time when he is an intern, relying upon informal advice received from fellow interns or resident physicians.

Even though medical certification of causes of death is very important, relatively little attention has been paid to the problem of improving its completeness and quality. The "Physician's Handbook on Medical Certification: Death, Fetal Death, Birth" (70), prepared by the National Center for Health Statistics and now in process of revision, is distributed through state health departments, but may not be at hand to individual physicians as they are completing death certificates. An instructional film for physicians on "Medical Certification of Causes of Death" is available for use by hospitals, medical schools, medical societies, health departments, and others interested in improving the quality of

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medical certification of causes of death. It is not known
how frequently it is used.

c.   Classification and Selection of Diabetes as a Cause of Death:

Mortality statistics for the United States, available
annually since 1900, are based on registered deaths classi-
fied by the International Classification of Diseases (ICD)
in accordance with the international rules for selecting the
cause of death.

The ICD is revised about once every ten years to keep
abreast of medical and statistical progress. The present
edition of the ICD is the Eighth Decennial Revision, to be
used until 1978 when the Ninth Revision will come into effect.

Many diseases and complications are usually involved in
death. However, it has been traditional to attribute the
death to a single cause, the disease that initiated the train
of events leading to death. This underlying cause concept
has been useful for the prevention of deaths, particularly
from the infectious diseases. However, for chronic diseases
it is frequently difficult to determine which of the diseases
started the events leading to death. The underlying cause
concept has been criticized in the past, but no adequate
substitute has yet been proposed for it.

One of the major objections to a single cause tabulation
is that a considerable amount of reported diagnostic data is
lost. For a disease like diabetes, this is very significant.
Diabetes is frequently the primary disease which gives rise
to the condition causing death, which may be direct compli-
cations of diabetes such as acidosis and coma, or cardiovas-
cular changes resulting from diabetes. Whether diabetes is
selected as the underlying cause of death or as the contribu-
tory cause of death depends on the way the medical certifi-
cation is made, with the medical certifier alone having respon-
sibility for designating the cause of death for primary mor-
tality tabulations. If it is his or her opinion that the
events leading to death were initiated by diabetes, then
diabetes will be coded as the underlying cause of death.

On the other hand, if the medical certifier determines
that diabetes only contributed to the death, this fact will
be noted. Further, if it is the judgment of the medical
certifier that diabetes was not directly or indirectly related
to the death, the disease will not be reported on the death
certificate. For example, in deaths from malignancies or from

violence, it would not be expected that diabetes would be specified. In other words, the presence of diabetes would not necessarily be indicated on death certificates if the disease was under control and not contributory to the death. The reporting problems make it impossible to obtain an estimate of mortality among diabetics from mortality statistics alone.

Through the Eighth Revision of the International Classification of Diseases, there have been no significant changes in the classification of diabetes. However, an important modification in the Sixth Revision in the method of selecting the underlying cause of death for primary mortality tabulations caused a drop of 36% in diabetes mortality in 1949. From 1949 on, there has been a large break in the continuity of the diabetes mortality trend, an artifact in the data which must be taken into account in the interpretation of time trends in diabetes mortality. Comparability ratios are available from the National Center for Health Statistics for each revision year since 1940.

The Ninth Revision of the ICD will provide details on the complications of diabetes which have not been available before. The following four digit subdivision has been proposed:

.0 Without mention of complication
.1 Nonclinical diabetes
.2 Diabetes with ketoacidosis
.3 Diabetes with coma
.4 Diabetes with renal manifestations
.5 Diabetes with ophthalmic manifestations
.6 Diabetes with neurological manifestations
.7 Diabetes with peripheral circulatory disorders
.8 Diabetes with other specified manifestations
.9 Diabetes with unspecified manifestations

Even these revisions will not make it possible to distinguish between juvenile- and adult-onset diabetes from the information on death certificates. This information will have to be obtained from a query to the attending physician.

The loss of diagnostic data under the single cause classification scheme has led to frequent suggestions for multiple cause tabulations. Because of the expense involved in coding and tabulating more than one cause of death and the difficulties in analyzing and reporting the data, multiple cause compilations in the United States have been attempted only six

times since 1900. Studies done in 1917, 1925, 1936, and 1940
were based on only two conditions, the underlying cause of
death and one associated cause. A 1955 study based on five
conditions -- the underlying cause and four associated causes --
produced very useful findings. The most recent study, based
on all conditions reported on death certificates in 1968,
contains imperfections, as it was carried out primarily to
provide the National Center for Health Statistics with coding
and tabulating experience. Beginning in 1969, the ACME
(Automated Classification of Medical Entities) system of
coding utilized in the 1968 study has provided the basis for
annual multiple cause tabulations.

d.   Problems in Residence Allocation:

     The following statement regarding geographic classification
is found in Vital Statistics Rates in the United States,
1900-1940, published more than 30 years ago, and including
one of the most thorough discussions of the basic qualifying
factors of vital statistics available (44). "The most impor-
tant single classification for mortality and natality data is
the classification by geographic units." This statement is
elaborated further:

     One of the primary purposes of the collection of vital
     statistics is to obtain data that make possible a
     comparison of death and birth rates between countries,
     states, cities, and other geographic units. Such
     comparisons are the first indicators of unusual mor-
     tality or natality conditions in any area, and there-
     fore stimulate and initiate subsequent series of tabu-
     lations, classifications, or investigations.

     In spite of the importance attributed to geographic
     classification and efforts at both the federal and state
     levels to improve the quality of geographic data, there is
     strong evidence that errors in classifying vital statistics
     data by place of residence still occur. Prior to 1940, most
     vital statistics data were classified according to place of
     occurrence, that is, to the geographic unit where the birth,
     death, etc. actually occurred. This "de facto" classifi-
     cation was not satisfactory for the U.S., where population
     data, the denominator in calculating rates, are tabulated
     by the Bureau of the Census on a "de jure" or place of
     residence basis. As a result, place of residence became the
     principal basis for classifying vital events. This is much
     more difficult than classifying by place of occurrence, where

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the place of death or birth is generally clearcut and determinable.

The determination of place of residence is dependent on the definition of residence and the information given on the certificate by the funeral director, member of the family, or other informant. These persons may not always know the exact limits of the minor civil division in which they live, or they may provide the post office address of the deceased -- which may differ from the actual place of residence. There are further problems if the last residence is temporary or if the deceased lived in a hospital, sanitorium, nursing home, or other institution at the time of death.

While these difficulties result in errors in residence allocation, the magnitude of the problem is largely unknown. The accuracy of information reported on vital records is not easy to measure and few studies deal specifically with the problem.

One of the notable efforts in the area of residence allocation is a comparison of the classification of residence stated on the death certificate with residence stated on the matching census record by the National Center for Health Statistics utilizing 1960 data (56). Findings in this study include the following:

1) "The classification of residence information on the death certificate corresponds closely to the residence on the census records for the decedents whose records were matched. The proportion of unmatched records was high -- 23 percent."

2) Based on a comparison of the results of the 1960 study and a matched record study involving births for 1950, "Considerable improvement in the quality of the residence data has taken place since 1950."

3) "An inverse relationship exists between the size of the geographic area and the degree of difference found between census assignments and those by NCHS."

4) "Compared with census assignments, NCHS somewhat overstates the numbers of deaths for individual urban places and understates those for rural areas."

5) NCHS had the greatest problem in properly allocating the residence of decedents in towns, townships, and boroughs in Connecticut, New Jersey, and Pennsylvania (almost three-fourths of the areas with large net

difference rates were towns or townships in these
three states); urban fringe areas; and territorial
annexations made between 1950 and 1960.

6) Results generally indicate that the annual death
rate for an individual urban place is slightly
overstated.

Factors stated to be related to the differences between
census and NCHS figures were (1) the difficulty in identify-
ing and coding towns, townships, and boroughs for vital
statistics purposes (duplication of place names within coun-
ties and double entries of place names on certificates con-
tributed to the problem); (2) problems presented by annexations,
in that the place names of the annexed areas are frequently
reported as the decedent's residence; and (3) unincorporated
areas which have mailing addresses and/or place names similar
to that of an adjacent urban place, which presented a coding problem.

Because mortality statistics are utilized for a variety
of purposes, possible inaccuracies in residence allocation
may be of minimal importance in some instances, while in
others, such as an epidemiologic investigation, they may be
extremely important. It is difficult, if not impossible, to
assess the overall impact of the problem, but it certainly
is considerable. How much time and money have been spent in
investigating the reasons for apparently high crude or cause-
specific death rates which are primarily the result of in-
accurate residence allocation? How many administrative and
other decisions are based on fallacious conclusions resulting
from inaccurate mortality data? What is the impact of these
decisions? These and numerous similar questions will have to
be answered in assessing the overall impact of the problem.
It is somewhat easier to provide specific examples of the
difficulties created by inaccurate residence allocation. In
a consumer survey of the uses and adequacy of national vital
statistics, one of the more frequently mentioned unmet needs was
for more detail on deaths for local areas (61). Despite this
expressed need for local data, NCHS, starting with data-year
1964, no longer separately identifies urban areas of 2,500-
10,000 because of the problem of properly identifying the
residence of decedents of such areas (44). This change was
effected primarily because the mailing address rather than
the actual residence of the decedent was often entered on the
death record. Thus, data users are deprived of needed data
from NCHS because of the residence allocation problem. If
such data are available from state sources, their accuracy
must also be questioned.

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One example of possible bias occasioned by inaccuracies in reporting residence is found in the Pennsylvania Department of Health Publication, Natality and Mortality Statistics, 1973 (52). Twenty-eight of the 29 cities (excluding Philadelphia, which is a consolidated city-county) have overall mortality rates higher than the state rate. The single exception is State College, a university town. A number of factors, including age and racial composition of the population and socioeconomic status, probably combine to create this situation, but errors in residence allocation cannot be discounted. It may be circumstantial, but Johnstown City, which had the highest all-cause death rate for the cities included, also had a very high net difference rate for deaths in the NCHS comparison study of 1960.

The potential impact of errors in residence reporting may be seen in the following example. In 1971, 12 infant deaths and 305 births were reported for Aliquippa Borough, Pennsylvania, a community of about 22,000 population (72). Investigation into the actual place of residence of mothers of infants who died revealed that five of the mothers actually lived outside the borough limits. Place of residence was incorrectly reported on two of the birth certificates. This reduced the infant death rate from 39.3 per 1,000 live births to approximately 23.1 This rate could not be determined precisely because it was not possible, in the time alloted, to determine if there were births or deaths that should have been allocated to Aliquippa but were allocated to some other geographic regions.

The above discussion sheds little light on the impact of the problem, but it should demonstrate the great need for caution in using mortality data obtained from death certificates. It is erroneous to interpret observed differences in terms of a specific factor or even a set of factors when other factors known to be related to the level of mortality, such as residence allocation, are not comparable.

4. DIABETES MORTALITY: UNDERLYING CAUSE OF DEATH

a. Historical Trends in the United States, 1900-1973:

Despite the fact that diabetes is extremely understated in traditional mortality tabulations, changing trends have been discerned several times during this century. The overall trend and those specific for age, race, or sex need to be

examined. Artificial changes in the level of diabetes mortality, due primarily to changes in the method of selecting the underlying cause of death, need to be taken into account when analyzing these trends.

The overall trend of diabetes mortality rose steadily between 1900 and 1940, with the death rate moving from 11 per 100,000 population in 1900 to 26 in 1940. It then leveled off at a rate of 25-27 during the years from 1940 to 1948. Over this period, five different revisions of the International Classification of Diseases (ICD) were used to classify deaths according to a single cause when more than one cause was reported on a death certificate. These revisions were made with the use of a Joint Cause Manual, which indicated which diseases had priority and should be selected over others when they appeared in combination on a death certificate. Under this system, diabetes had a very high priority and was frequently selected as the cause to the tabulated when other conditions were present. The sixth revision of the ICD, in 1949, did not make use of the Joint Cause Manual. The underlying cause concept was used for the first time in 1949. Under it, the condition that originated the chain of events which led to death was selected for tabulation. As a result of this change, there was a drop in diabetes mortality between 1948 and 1949 of about 40%.

This discussion of the break in comparability of diabetes death rates between 1948 and 1949 applies equally well to all of the other trends that will be discussed later. No further discussion on comparability will appear in the sections dealing with trends by sex, race, and age.

Between 1949 and 1967, diabetes death rates remained fairly constant within the 15 to 17 per 100,000 range. From 1968 to 1973, there has been a slight drop (about 5%) in diabetes death rates in the United States.

The trend of the diabetes death rate for males was steadily upward between 1930 and 1940, increasing from 15 to 20 per 100,000. From 1940 to 1948, the rate was basically unchanged, but a slight upward trend began in 1960 and lasted until 1967. During the 1950's, the rates were in the 12 to 13 per 100,000 range, but by 1967 they had risen to 15 per 100,000. They remained at this level through 1973. The rates for females followed essentially the same pattern except there was no rise during the 1960-1967 period. As shown in the following table, the crude diabetes death rates for females were consistently higher than those for males:

Year	Males	Females
1930–1940	15 to 20 per 100,000	23 to 33 per 100,000
1940–1948	19 to 20	31 to 33
1949–1959	12 to 13	19 to 20
1960–1967	13 to 15	19 to 20
1968–1973	15	21

The trend for white persons moved steadily upward during the 1930's. However, beginning in 1940, the rate leveled off and has varied little over the next 34 years. The trend for nonwhite persons was the same except that their rates rose steadily between 1957 and 1967. During most of this century, the rate for nonwhite persons was lower than the rate for whites. This pattern changed during the 1960's and now the rate for nonwhites is the higher of the two. The rates are shown in the following table:

Year	White	Nonwhite
1930–1940	20 to 28 per 100,000	13 to 18 per 100,000
1940–1948	26 to 28	16 to 19
1949–1956	16 to 17	14
1957–1967	16 to 17	15 to 21
1968–1973	17 to 18	23

The trends by _age_ will be looked at for the 1949–1967 period (Table 1). It will be remembered that the overall trend for these years was level. A steep decline occurred in the death rate for persons under one year of age from 0.7 to 0.4 per 100,000, mostly between 1950 and 1953. The rate has been fairly stable ever since. Each of the age groups 1–4, 5–14, and 15–24 years showed a substantial decline. Persons aged 25–34 and 45–54 years had relatively unchanged rates over this period, while those aged 35–44 years experienced a slight rise. The rates for persons aged 55–64 years dropped. This was mainly due to sharp decline between 1950 and 1954. Persons aged 65–74 years had their rates decline through 1959 and then level off during the 1960's. Those 75–84 years old saw their rates drop from 1949 to 1957 but increase from 1958 to 1967. The net result was that the rates at the end of the period were slightly higher than they were at the beginning. Persons aged 85 years and over experienced a large increase in their rates (over 50%). This consisted of a small rise from 1949 to 1959 and an extremely rapid rise from 1960 to 1967. The direction of the trend and the level of the rates during this period are shown on the next page:

TABLE 1

AGE-SPECIFIC DEATH RATES PER 100,000 POPULATION FOR DIABETES MELLITUS: UNITED STATES, 1950-1973

	TOTAL	\-1	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
						Age (In Years)						
1973--------	18.2	0.5	0.1	0.2	0.6	2.0	4.6	11.8	34.1	85.4	179.7	245.9
1972--------	18.6	0.5	0.2	0.2	0.6	2.4	4.9	12.3	33.8	89.7	181.5	255.3
1971--------	18.6	0.6	0.1	0.2	0.6	2.3	5.1	12.4	35.2	89.5	182.4	248.0
1970--------	18.9	0.3	0.2	0.3	0.7	2.2	5.3	12.8	36.7	92.1	186.8	230.2
1969--------	19.1	0.3	0.1	0.2	0.7	2.5	5.4	13.1	37.1	96.7	185.9	262.0
1968--------	19.2	0.5	0.1	0.2	0.7	2.6	5.3	13.0	39.2	99.5	183.3	258.3
1967--------	17.7	0.4	0.1	0.2	0.7	2.5	4.8	12.3	36.2	94.2	169.4	234.8
1966--------	17.7	0.5	0.2	0.3	0.7	2.6	5.0	12.1	35.7	95.7	171.5	234.4
1965--------	17.1	0.5	0.2	0.3	0.7	2.6	4.7	11.9	36.1	92.6	166.4	220.0
1964--------	16.9	0.6	0.2	0.3	0.8	2.6	4.8	12.0	37.3	91.4	161.6	204.9
1963--------	17.2	0.4	0.2	0.3	0.9	2.6	5.0	12.1	37.5	95.1	165.9	206.6
1962--------	16.8	0.6	0.2	0.3	0.8	2.5	4.6	11.7	36.9	94.0	160.2	206.7
1961--------	16.4	0.3	0.2	0.3	0.7	2.7	4.7	11.3	35.9	91.4	162.9	184.2
1960--------	16.7	0.4	0.3	0.4	0.9	2.3	4.5	12.1	37.9	93.4	163.7	181.7
1959--------	15.9	0.3	0.2	0.4	0.9	2.6	3.8	11.4	37.5	89.9	154.5	158.8
1958--------	15.9	0.3	0.3	0.3	0.9	2.5	4.1	11.2	37.0	91.6	151.7	169.9
1957--------	16.0	0.3	0.3	0.4	1.2	2.6	4.5	11.2	38.0	92.5	149.8	158.1
1956--------	15.7	0.5	0.2	0.3	1.0	2.4	3.8	11.0	37.5	92.1	151.7	162.6
1955--------	15.5	0.6	0.3	0.4	1.0	2.4	3.9	10.9	37.3	91.7	150.6	163.1
1954--------	15.6	0.5	0.3	0.4	1.0	2.2	3.9	11.3	38.3	92.3	153.9	155.3
1953--------	16.3	0.5	0.3	0.4	1.2	2.4	4.1	11.7	41.7	96.2	161.7	156.4
1952--------	16.4	0.8	0.5	0.6	1.3	2.3	4.0	12.3	40.8	99.7	161.5	152.8
1951--------	16.3	0.4	0.4	0.5	1.2	2.2	3.9	12.4	42.7	99.8	161.2	151.1
1950--------	16.2	0.7	0.3	0.6	1.1	2.2	4.2	12.4	42.1	101.2	166.7	150.3

Source: National Center for Health Statistics

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Age	Direction	Rate
All ages	Level	17–18
Under 1	Down	0.7–0.4
1–4	Down	0.3–0.1
5–14	Down	0.6–0.2
15–24	Down	1.1–0.7
25–34	Level	2.2–2.7
35–44	Slight rise	4–5
45–54	Level	11–12
55–64	Drop	42–36
65–74	Drop 1949–1959	101–90
	Level 1960–1967	92–95
75–84	Drop 1949–1957	167–150
	Rise 1958–1967	151–170
85 and over	Slight rise 1949–1959	150–159
	Sharp rise 1960–1967	181–235

In order to account for age changes over time or differences
between race-sex groups, age-adjusted diabetes death rates were
computed for the United States. As can be seen in Table 2, the
age-adjusted rates have changed in a somewhat erratic manner.
In 1973, it was 13.2 per 100,000 of the total population,
representing a 1.1% decrease from the 1950 rate of 14.3
per 100,000. During the 1950–1973 period, the rates increased
among white males from 11.3 to 12.0 per 100,000, among nonwhite
males from 11.8 to 21.1 per 100,000, and among nonwhite females
from 22.6 to 28.6 per 100,000. During the same period, a
dramatic 30% decrease from 16.4 to 11.6 per 100,000 was
reported among white females.

The age-adjusted death rates were consistently highest for
nonwhite females, and by 1973 they were more than twice the
comparable figures for white females. It is noteworthy that,
within the white population, the traditional sex difference
in the diabetes mortality rate (females > males) was actually
reversed beginning with 1971. This significant change in the
trend was not manifest in the nonwhite population, however.

b. Geographic Variations in Diabetes Mortality

1) International Differences: Mortality data by diagnosis
   and sex are available for a limited number of countries.
   A comparison of age-adjusted statistics for 1957–58 and
   1967–68 for the United States, Canada, and 13 European
   nations indicated that the diabetes death rates on the

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TABLE 2

AGE-ADJUSTED DEATH RATES FOR DIABETES MELLITUS BY RACE AND SEX: UNITED STATES, 1950-1973

Rate per 100,000 population

	TOTAL			WHITE			ALL OTHER		
	BOTH SEXES	MALE	FEMALE	BOTH SEXES	MALE	FEMALE	BOTH SEXES	MALE	FEMALE
1973--------	13.2	12.9	13.3	11.8	12.0	11.6	25.3	21.1	28.6
1972--------	13.6	13.2	13.9	12.2	12.3	12.1	26.0	21.2	30.1
1971--------	13.7	13.2	14.0	12.4	12.4	12.3	25.7	20.4	30.2
1970--------	14.1	13.5	14.4	12.9	12.7	12.8	25.2	20.4	29.3
1969--------	14.5	13.6	15.1	13.2	12.8	13.3	27.7	21.3	33.2
1968--------	14.7	14.0	15.3	13.4	13.2	13.5	28.0	21.3	33.7
1967--------	13.7	12.9	14.4	12.7	12.4	12.8	24.5	18.5	29.7
1966--------	13.9	12.8	14.6	12.7	12.3	13.0	24.8	18.3	30.5
1965--------	13.5	12.5	14.4	12.5	11.9	12.9	23.6	18.1	28.6
1964--------	13.5	12.4	14.4	12.5	11.8	12.9	23.6	17.6	29.0
1963--------	13.8	12.4	14.9	12.7	11.9	13.3	23.1	16.6	29.1
1962--------	13.5	12.3	14.5	12.5	11.8	13.1	21.8	16.1	27.1
1961--------	13.3	11.7	14.6	12.5	11.4	13.3	21.0	14.9	26.7
1960--------	13.6	12.0	15.0	12.8	11.6	13.7	21.6	16.1	26.8
1959--------	13.0	11.3	14.5	12.4	11.0	13.5	19.4	14.1	24.2
1958--------	13.0	11.3	14.6	12.5	11.1	13.6	18.8	13.0	24.3
1957--------	13.2	11.1	15.2	12.7	10.9	14.3	18.2	12.5	23.6
1956--------	13.0	11.0	14.8	12.6	10.9	14.0	17.1	11.7	22.2
1955--------	13.0	10.9	14.8	12.6	10.9	14.1	16.5	11.2	21.6
1954--------	13.1	10.9	15.2	12.8	10.9	14.5	16.4	11.3	21.2
1953--------	13.9	11.2	16.3	13.5	11.2	15.6	17.2	11.3	22.9
1952--------	14.1	11.5	16.4	13.8	11.5	15.8	16.5	11.5	21.5
1951--------	14.2	11.3	16.9	13.9	11.2	16.4	16.6	11.8	21.3
1950--------	14.3	11.4	17.1	13.9	11.3	16.4	17.2	11.8	22.6

Source: National Center for Health Statistics.

average had increased 42% for males and 46% for females
(Table 3). Every country but one (Norway) reported a
rise in the mortality rate for at least one sex, and all
except three others (United States, England, and Wales)
reported increased rates for both males and females. How-
ever, despite this consistent trend, rates varied among
nations, with the highest about three times as great as
the lowest.

In 1957-58, male death rates ranged from 3.7 per
100,000, reported for England and Wales, to 11.4 in the
United States. For females, the range was from 5.3 in
Denmark to 17.5 in Belgium. In 1967-68, male rates
ranged from 4.5 in Norway to 13.9 in Belgium, while female
rates ranged from a low of 4.4 in Norway to a high of 23.4
in Belgium. Reasons for these marked differences between
nations and changes over time should be investigated,
focusing on accuracy in reporting and consistency in
coding, as well as possible cultural and etiologic factors.

2) United States Differences by Regions and States: Within
    the United States, the age-adjusted diabetes death rates
    during the period 1969-71 differed substantially from one
    state to another, ranging from the lowest, 6.7 per 100,000
    in Alaska, to the highest, 22.0 per 100,000 in Delaware
    (Table 4). In general, the age-adjusted rates were higher
    in the eastern and central states and lower in the mountain
    and Pacific states. In most states, the reported rates
    were higher for females than for males and also higher for
    nonwhites than for whites. In 28 states, nonwhite rates
    were at least double the comparable figures for whites.
    The reasons for these observed differences between the
    states and between race-sex groups are not completely
    understood at present.

3) Pennsylvania Differences by Selected Local Areas: In a
    1972 study of diabetes mortality in Pennsylvania, which
    included all minor civil subdivisions with a population of
    5,000-99,999 (232 cities and boroughs and 228 townships),
    the average annual diabetes death rate per 100,000 popu-
    lation for the period 1967-1971 was 23.1, with the rate
    30.9 for cities and boroughs and 15.3 for townships (77).
    Since the median ages of the township populations were
    generally lower for the cities and boroughs, it was felt
    that this might account for the difference in rates.

Although it was not practical to calculate age-adjusted
rates for all of these communities, it was possible to

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TABLE 3

MORTALITY FROM DIABETES
UNITED STATES, CANADA, AND SELECTED EUROPEAN COUNTRIES
1957-58 and 1967-68

| | Average Annual Death Rate per 100,000 | | | | | |
| | 1957-58 | | 1967-68 | | % Increase | |
Country	Male	Female	Male	Female	Male	Female
United States						
White	11.2	14.2	13.1	13.6	17	-4
Nonwhite	13.6	25.4	19.9	31.6	46	24
Total.	11.4	15.2	13.5	14.9	18	-2
Canada.	9.4	11.9	11.6	12.6	23	6
Denmark.	4.5	5.3	8.4	8.5	87	60
Norway.	4.6	5.8	4.5	4.4	-2	-24
Sweden..	7.0	8.3	10.5	10.9	50	31
Netherlands	7.5	14.1	9.1	15.1	21	7
Weighted Average. .	6.5	9.9	8.8	11.5	35	16
United Kingdom						
England & Wales . .	3.7	6.1	5.0	5.6	35	-8
Northern Ireland. .	4.2	5.4	5.0	6.8	19	26
Scotland	4.9	8.6	7.2	9.0	47	5
Ireland	5.1	5.6	5.9	6.9	16	23
Belgium	10.3	17.5	13.9	23.4	35	34
France	6.9	7.8	9.8	10.0	42	28
Germany, Fed. Rep. . .	6.6	9.3	9.0	11.6	36	25
Switzerland	7.7	9.8	12.0	14.1	56	44
Weighted Average ..	6.0	8.4	8.4	10.1	40	20
Italy	7.3	9.5	11.4	15.6	56	64
Spain	6.4	8.9	7.7	10.2	20	15
Portugal	6.1	5.8	7.6	8.0	25	38
Weighted Average . .	6.9	8.9	9.8	13.0	42	46

*Adjusted on basis of age distribution of the United States total Population
1940. (Minus sign - denotes decrease.)

Source: Reports of Division of Vital Statistics, National Center for Health
Statistics; World Health Statistics Annuals, World Health Organization; and
Demographic Yearbook, Statistical Office of the United Nations.

TABLE 4

ANNUAL AGE-ADJUSTED DIABETES MORTALITY RATES PER 100,000 POPULATION BY RACE AND SEX
UNITED STATES, EACH STATE AND REGION, 1969-71

	TOTAL	MALE	FEMALE	WHITE	NON-WHITE
UNITED STATES	14.1	13.5	14.5	12.8	25.9
NEW ENGLAND	13.6	13.7	13.3	13.4	21.4
MAINE	13.1	12.5	13.5	13.0	39.7
NEW HAMPSHIRE	15.2	14.2	16.1	15.2	18.2
VERMONT	11.9	12.0	11.7	11.8	36.2
MASSACHUSETTS	13.3	14.2	12.5	13.1	21.7
RHODE ISLAND	18.2	16.8	19.1	18.1	26.2
CONNECTICUT	12.6	12.5	12.5	12.4	20.1
MIDDLE ATLANTIC	15.2	14.5	15.6	14.2	26.0
NEW YORK	14.3	14.2	14.2	13.2	26.0
NEW JERSEY	15.6	14.5	16.3	14.5	27.9
PENNSYLVANIA	16.4	14.8	17.4	15.7	25.1
EAST NORTH CENTRAL	16.1	15.6	16.4	15.2	26.4
OHIO	17.0	16.2	17.5	16.3	25.5
INDIANA	15.6	14.7	16.2	15.0	25.5
ILLINOIS	13.3	12.9	13.6	12.3	22.5
MICHIGAN	20.2	19.9	20.5	18.8	33.2
WISCONSIN	14.4	14.4	14.4	14.2	25.6
WEST NORTH CENTRAL	12.8	12.5	12.9	12.2	26.8
MINNESOTA	11.1	11.3	10.9	11.0	22.2
IOWA	12.1	11.4	12.7	12.1	19.8
MISSOURI	14.8	14.0	15.5	13.7	27.5
NORTH DAKOTA	12.1	11.7	12.5	11.4	63.7
SOUTH DAKOTA	11.8	11.8	11.8	11.1	35.8
NEBRASKA	11.9	13.2	10.7	11.6	27.7
KANSAS	12.7	12.8	12.5	12.3	22.7
SOUTH ATLANTIC	14.4	13.6	15.1	11.4	29.0
DELAWARE	22.0	20.5	23.4	19.9	36.9
MARYLAND	18.6	16.5	19.9	16.1	32.6
DISTRICT COLUMBIA	21.3	23.6	19.4	10.1	30.6
VIRGINIA	12.4	11.7	12.9	10.0	23.6
WEST VIRGINIA	13.0	10.4	15.2	12.0	34.9
NORTH CAROLINA	15.4	15.0	15.7	12.1	28.7
SOUTH CAROLINA	19.3	17.0	21.0	14.5	32.6
GEORGIA	15.5	14.8	16.0	11.6	28.6
FLORIDA	11.1	11.0	11.3	9.0	29.1

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	TOTAL	MALE	FEMALE	WHITE	NON-WHITE
EAST SOUTH CENTRAL	14.4	13.0	15.5	11.9	26.0
KENTUCKY	15.1	14.4	15.6	13.9	31.8
TENNESSEE	12.4	11.4	13.1	10.3	24.7
ALABAMA	14.9	13.2	16.3	11.7	25.1
MISSISSIPPI	16.3	13.5	18.5	11.5	26.2
WEST SOUTH CENTRAL	14.3	12.8	15.6	12.2	27.4
ARKANSAS	11.9	10.1	13.5	10.2	36.4
LOUISIANA	21.4	18.2	24.0	15.9	36.4
OKLAHOMA	11.7	11.7	11.6	10.5	23.4
TEXAS	13.4	12.1	14.5	12.1	23.4
MOUNTAIN	11.9	12.0	11.8	11.4	25.1
MONTANA	12.0	13.8	10.2	11.6	26.3
IDAHO	12.5	11.6	13.3	12.5	16.2
WYOMING	10.0	9.0	10.8	9.6	29.8
COLORADO	9.7	8.7	10.5	9.6	15.3
NEW MEXICO	14.9	14.5	15.3	14.0	28.2
ARIZONA	11.0	11.9	10.1	10.0	26.8
UTAH	14.9	15.6	14.3	14.6	33.6
NEVADA	14.4	14.5	14.4	13.5	32.0
PACIFIC	10.4	10.6	10.3	9.9	17.2
WASHINGTON	12.0	12.2	11.8	11.9	20.5
OREGON	9.7	9.6	9.7	9.5	15.8
CALIFORNIA	10.1	10.3	9.9	9.5	17.2
ALASKA	6.7	6.3	7.1	8.9	1.6
HAWAII	16.5	16.2	17.1	14.1	17.6

group them according to median age. The death rate was found to increase consistently as the median age increased; this occurred for both types of communities, cities-boroughs and townships. However, the mortality rates at each median age group were higher for cities-boroughs than for townships. The same pattern of difference also existed in mortality from all causes, although the relative difference was considerably greater with respect to diabetes.

Of the 232 cities and boroughs included in the above analysis, 108 had diabetes death rates higher than 30 per 100,000, while only 17 of the 228 township rates were this high. The national average for this period was approximately 18 per 100,000 population. Factors other than problems in residence allocation certainly account for some of the discrepancy, but it is not possible to determine at the present time how much each contributes.

DIABETES MORTALITY: MULTIPLE CAUSE OF DEATH

a.   United States Mortality, 1955 and 1968:

Since diabetes loses much of its visibility when only underlying causes of death data are considered, it is appropriate to look at the most recent years for which multiple cause of death data have been tabulated. In 1955, the deaths of 25,217 persons were coded to diabetes as the underlying cause, and an additional 36,692 persons had diabetes mentioned on their death certificate but the cause of death was coded to some other cause. In 1968, the corresponding figures were 38,352 and 91,602, respectively. Thus, in 1955, more than 40% of all certificates that mentioned diabetes were coded to it, while in 1968 this figure dropped to less than 30%.

In 1955, there were 1,527,691 deaths with 2,911,034 conditions reported on their certificates. In 1968, the corresponding figures were 1,930,082 and 4,587,343, respectively. The percentage distribution of the number of conditions reported on each certificate for all deaths and those coded to diabetes was as follows:

Number of Conditions	1955 All Deaths	1955 Diabetes	1968 All Deaths	1968 Diabetes
1	42.2	5.1	26.4	4.6
2	34.4	35.2	35.0	21.8
3	17.0	40.1	24.2	43.0
4	5.0	14.7	10.2	20.8
5 or more	1.4	4.9	4.1	9.9

From the above, it can be seen that more conditions are reported on the certificates of persons dying of diabetes than on those of the average death. Also more conditions were reported in 1968 than in 1955. It is interesting to note that, about 5% of the time in both years, diabetes was the only condition mentioned on the death certificate of persons dying from diabetes. Other than the drop in the percentage of deaths assigned to diabetes when it is mentioned, there has been little shift in the causes assigned as underlying under these circumstances. The percentage of deaths assigned to selected causes of death when diabetes is mentioned follows:

	1955	1968
Diabetes	40.7	29.9
Heart disease	45.3	40.1
Cerebrovascular disease	9.5	11.3
Malignant neoplasms	5.5	6.1
Accidents	1.2	0.7

On the other hand, when diabetes was selected as the underlying cause of death, other conditions were frequently mentioned with it. Sometimes several conditions of a given type were reported on the same certificate. For example, two different kinds of heart disease might be reported along with diabetes on a certificate. The percentage distribution of these conditions is as follows:

	1955	1968
Heart disease	59.9	56.6
Arteriosclerosis	24.9	22.4
Cerebrovascular disease	21.5	21.7
Influenza and pneumonia	5.9	8.5
Malignant neoplasms	1.6	2.1
Cirrhosis	0.7	1.0
Bronchitis, emphysema, and asthma	0.3	1.0

Again, the distribution has changed little over the 13-year period.

The ages of persons with diabetes mentioned on their death certificates increased between 1955 and 1968, as the following table shows:

	1955	1968
Under 1	0.0	0.0
1-14	0.3	0.1
15-44	4.1	2.8
45-64	29.3	23.9
65-84	61.4	64.2
85 and over	4.8	9.0

There were declines in the percentages of deaths in all age groups below 65 and increases above that age in 1968, compared with 1955. By race and sex, females tended to be older than males and whites older than nonwhites in both years. Each of the four race-sex groups showed an increase in the average age at death between 1955 and 1968 similar to that shown by the total population.

b. Pennsylvania Mortality, 1968 and 1969:

A recent study (80) of 200,000 death certificates filed in Pennsylvania during the 1968-1969 period indicates that diabetes was mentioned on a total of 10,170 certificates. Of this total, 2,639 (26%) specified diabetes as the underlying cause, whereas the remaining 7,531 listed diabetes as a contributory cause (Table 5). In order to evaluate the nature and extent of coexisting and/or diabetic complications, a detailed analysis was made of multiple causes of death recorded on those 10,170 death certificates which mentioned diabetes (Table 6).

By far, the largest proportion (60%) of other diseases reported with diabetes was represented by a group of circulatory disorders, which included major cardiovascular diseases (45%), cerebrovascular diseases (11%), hypertension (1%), and arteriosclerosis (1%). The most common forms of heart disease were coronary occlusion and myocardial infarction. Other major causes of death among diabetics were cancer (6%), influenza and pneumonia (3%), diseases of the kidney (1%), and cirrhosis of the liver (1%) -- in decreasing frequency.

The constellation of multiple causes of death among diabetics has changed considerably during the past decade.

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TABLE 5

DIABETES MELLITUS AS UNDERLYING AND CONTRIBUTORY CAUSE OF DEATH: NUMBER, RATE, AND
PERCENT, BY SEX AND RACE: PENNSYLVANIA, MAY 1968-APRIL 1969

Cause of Death	Total	White Male	Female	Nonwhite Male	Nonwhite Female
			Number		
Diabetes Mellitus, Total Reported	10,170	3,735	5,763	227	445
Underlying Cause of Death	2,639	927	1,472	76	164
Contributory Cause of Death	7,531	2,808	4,291	151	281
		Rate Per 100,000 Population			
Diabetes Mellitus, Total Reported	86.2	72.3	103.5	45.8	79.4
Underlying Cause of Death	22.4	17.9	26.4	15.3	29.3
Contributory Cause of Death	63.9	54.3	77.1	30.4	50.2
			Percent		
Diabetes Mellitus, Total Reported	100.0	100.0	100.0	100.0	100.0
Underlying Cause of Death	25.9	24.8	25.5	33.5	36.9
Contributory Cause of Death	74.1	75.2	74.5	66.5	63.1

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Underlying Cause of Death		All Races Both Sexes	White	Nonwhite	Male	Female
		Number				
All causes		10,170	9,498	672	3,962	6,208
Malignant neoplasms	140-209	571	548	23	244	327
Diabetes mellitus	250	2,639	2,399	240	1,003	1,636
Diseases of the circulatory system	390-458	6,066	5,738	328	2,285	3,781
Diseases of heart	390-398,402, 404,410-429	4,604	4,376	228	1,784	2,820
Hypertension	400,401,403	65	59	6	24	41
Cerebrovascular disease	430-438	1,083	1,006	77	367	716
Diseases of arteries, arterioles and capillaries	440-448	217	211	6	79	138
Arteriosclerosis	440	142	137	5	46	96
Diseases of veins and lymphatics, and other diseases of circulatory system	450-458	97	86	11	31	66
Veinous thrombosis and embolism	450-453	94	83	11	30	64
Diseases of the respiratory system	460-519	354	319	35	191	163
Cirrhosis of liver	571	64	60	4	43	21
Diseases of genitourinary system	580-629	140	132	B	66	74
Nephritis and nephrosis	580-584	45	41	4	21	24
Infections of kidney	590	55	51	4	26	29
All other causes	Residual	336	302	34	130	206
		Percent				
All causes		100.0	100.0	100.0	100.0	100.0
Malignant neoplasms	140-209	5.6	5.8	3.4	6.2	5.3
Diabetes mellitus	250	25.9	25.3	35.7	25.3	26.4
Diseases of the circulatory system	390-458	59.6	60.4	48.8	57.7	60.9
Diseases of heart	390-398,402, 404,410-429	45.3	46.1	33.9	45.0	45.4
Hypertension	400,401,403	0.6	0.6	0.9	0.6	0.7
Cerebrovascular disease	430-438	10.6	10.6	11.5	9.3	11.5
Diseases of arteries, arterioles and capillaries	440-448	2.1	2.2	0.9	2.0	2.2
Arteriosclerosis	440	1.4	1.4	0.7	1.2	1.5
Diseases of veins and lymphatics, and other diseases of circulatory system	450-458	1.0	0.9	1.6	0.8	1.1
Venous thrombosis and embolism	450-453	0.9	0.9	1.6	0.8	1.0
Diseases of the respiratory system	460-519	3.5	3.4	5.2	4.8	2.6
Cirrhosis of liver	571	0.6	0.6	0.6	1.1	0.3
Diseases of genitourinary system	580-629	1.4	1.4	1.2	16.7	1.2
Nephritis and nephrosis	580-584	0.4	0.4	0.6	0.5	0.4
Infections of kidney	590	0.5	0.5	0.6	0.7	0.5
All other causes	Residual	3.3	3.2	5.1	3.3	3.3

Comparable data for the U.S. as of 1955 (85) were analyzed
and reported by the Department of Health, Education, and
Welfare.

During the 1955 calendar year, attending physicians cer-
tified diabetes as the underlying cause of death in 25,217
persons in the United States (Table 7). However, of all
death certificates mentioning diabetes as a cause of death,
41% designated diabetes as the underlying cause; included in
the remaining 59% were arteriosclerotic heart disease, includ-
ing coronary (25%); hypertension with heart disease (5%); all
other major cardiovascular-renal diseases (7%); cancer (6%);
and others (5%).

. Comparing the 1968-1969 Pennsylvania data with the 1955
United States data with respect to multiple causes of death
among diabetics, it is clear that the proportion of diabetic
patients for whom diabetes was listed as the underlying cause
of death decreased from 41% to 26%.

6. LIFE EXPECTANCY AND SURVIVAL AMONG DIABETICS

One important consideration in the evaluation of diabetes mortality
may be generally expressed in the following related questions:
(1) Is the life expectancy among diabetics the same as for nondiabetics
(2) Are there specific causes which are responsible for excessive
mortality among diabetics?   (3) What are the differences in the sur-
vival function between diabetics with complications and those without
complications?

If any cause of death could be completely eliminated, there would
be a rise in life expectancy as a result. Life tables projecting such
a rise were prepared using 1959-1961 data for several selected causes
of death, including diabetes. If diabetes were to be eliminated as a
cause of death, the life expectancy of the total population in this
three-year period would have increased 0.22 years at birth. This in-
crease would have applied at all ages through 25, at which time a long,
slow reduction in the increase would have begun. By age 85, this
increase would have been reduced to only 0.03 years. The increases
by race and sex are shown below:

	White	Nonwhite
Male	0.15	0.18
Female	0.27	0.42

Thus, the elimination of diabetes as a cause of death would benefit
females more than males and nonwhites more than whites.

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TABLE 7: CAUSES OF DEATH OF PERSONS WHOSE DEATH CERTIFICATES
MENTION DIABETES, UNITED STATES, 1955

Underlying (principal) cause of death	Diabetics	
	Number	Percent
Total number death certificates with mention of diabetes . . . . [1]	61,754	100.0
Diabetes (260).	25,217	40.8
Other, total.	36,537	59.2
Infective and parasitic diseases (001-138).	490	0.8
Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues (140-205)	3,421	5.5
Major cardiovascular-renal diseases (330-334, 400-468, 592-594).	28,063	45.4
Vascular lesions affecting central nervous system (330-334)	5,903	9.6
Rheumatic fever and chronic rheumatic heart disease (400-402, 410-416).	276	0.4
Arteriosclerotic heart disease, including coronary disease (420)	15,124	24.5
Nonrheumatic chronic endocarditis, and other myo-cardial degeneration (421-422).	1,498	2.4
Other diseases of heart (430-434)	302	0.5
Hypertension with heart disease (440-443)	2,934	4.7
Hypertension without mention of heart (444-447) . .	392	0.6
General arteriosclerosis (450).	744	1.2
Other diseases of circulatory system (451-468). . .	241	0.4
Chronic and unspecified nephritis and other renal sclerosis (592-594)	649	1.1
Influenza and pneumonia, except pneumonia of newborn (480-493).	975	1.6
Accidents and other violence (E800-E999).	780	1.3
Other diseases (Residual).	2,808	4.6

[1] More persons with diabetes died during 1955 than the vital statistics
show, because: (a) A large number of death certificates show only one
condition. (b) Doctors are not required to record diabetes if they do
not feel that it contributed to the death.

Source: Vital Statistics of the United States, 1955, Supplement. U.S.
Department of Health, Education, and Welfare, 1965. Washington:
U. S. Government Printing Office.

Also, a person born during this period had a probability of eventually dying from diabetes of 0.017. The race-sex specific probabilities are shown below:

	White	Nonwhite
Male	0.013	0.013
Female	0.023	0.027

This reflects the greater incidence and mortality rates from diabetes among females.

At the same time, the proportion of other diseases listed as the underlying causes of death increased from 59 to 74%. Most of this increase was attributed to the broad category of heart disease, and, to a certain extent, reflects the fact that the U.S. population has been growing older. Prior to 1955, most known diabetics were symptomatic, with elevated fasting and postprandial glucose. Since 1968, many more diabetics are asymptomatic and discovered by screening tests.

The proportion of underlying causes of death by cancer and cerebrovascular and renal diseases remained virtually unchanged, however. This suggests that certain factors other than an aging population have also influenced the observed historical change in the configuration of multiple causes of death among diabetics. It is not immediately clear how much of this historical change was due to a change in the true incidence of heart disease, or how much by a factor such as biased or preferential reporting of heart disease as the underlying cause of death.

Although many diseases are associated with diabetes, as presented in the Pennsylvania study (80) and elsewhere, the extent and nature of such an association by specific disease category have not been evaluated critically. To provide more insight into this association, diabetic patients were compared with matched nondiabetic patients in terms of relative frequency of various coexisting diseases. For the purpose of this comparison, the data from special mail questionnaires from certifying physicians were used (Table 8). Several interesting findings emerged from this analysis. First, of the ten categories of diseases compared, all except diseases of the liver and "other diseases" were more prevalent among diabetic patients than among nondiabetic patients.

Second, in terms of the relative frequency of mention, heart disease ranked the highest (88% diabetics vs. 75% nondiabetics), and then in decreasing order, hypertension (51% diabetics vs. 34% nondiabetics), obesity (39% diabetics vs. 21% nondiabetics), peripheral vascular disease (32% diabetics vs. 27% nondiabetics, generalized arteriosclerosis (28% diabetics vs. 21% nondiabetics), kidney disease

TABLE 8

DEATH CERTIFICATES AND QUESTIONNAIRES OF 282 DIABETICS (RANDOM SAMPLE) AND 263 MATCHED CONTROLS
WITH MENTION OF SELECTED PHYSICAL CONDITIONS: PENNSYLVANIA MAY 1968-APRIL 1969

Physical Conditions Mentioned On:

Physical Conditions	Either Death Certificate or Questionnaire		Death Certificate		Questionnaire	
	Diabetics	Controls	Diabetics	Controls	Diabetics	Controls
				Number		
Obesity	109	55	8	1	109	55
Liver disease	16	33	7	11	14	33
Hypertension	145	89	37	18	139	86
Heart disease	247	197	202	164	208	187
Retinopathy	75	23	–	1	75	23
Cerebrovascular disease	121	91	66	53	105	84
Peripheral vascular disease	89	72	15	14	87	67
Generalized arteriosclerosis	80	56	69	43	37	32
Renal disease	78	38	31	16	70	35
Other disease	147	181	101	137	105	168
				Proportion		
Obesity	0.39	0.21	0.03	0.00	0.39	0.21
Liver disease	0.06	0.13	0.02	0.04	0.05	0.13
Hypertension	0.51	0.34	0.13	0.07	0.49	0.33
Heart disease	0.88	0.75	0.72	0.62	0.74	0.71
Retinopathy	0.27	0.09	–	0.00	0.27	0.09
Cerebrovascular disease	0.43	0.35	0.23	0.20	0.37	0.32
Peripheral vascular disease	0.32	0.27	0.05	0.05	0.31	0.25
Generalized arteriosclerosis	0.28	0.21	0.24	0.16	0.13	0.12
Renal disease	0.28	0.14	0.11	0.06	0.25	0.13
Other disease	0.52	0.69	0.36	0.52	0.37	0.64

Notes: (1) Matching criteria used include age, sex, race, county of occurrence, and month of death of the patient.
(2) Number of diabetics = 282 (random sample); the original random sample included 311 patients, but 29 did not provide information.
(3) Number of controls = 263 (matched); the original matched controls included 311 patients, but 48 did not provide information.

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(28% diabetics vs. 14% nondiabetics), retinopathy (27% diabetics vs. 9% nondiabetics), and cerebrovascular disease (43% diabetics vs. 35% nondiabetics).

Third, differences between diabetics and nondiabetics were highly significant statistically with respect to the presence of heart disease, hypertension, obesity, retinopathy, and kidney disease; the probability of all these differences being due to chance was less than one in 10,000. In terms of the excess risk manifested among diabetic patients, as compared with nondiabetics, retinopathy was the most important; specifically, the risk of diabetics having retinopathy was 200% greater. In decreasing order, the excess risk was 100% for kidney disease, 86% for obesity, 50% for hypertension, and 17% for heart disease.

Fourth, differences between diabetics and nondiabetics with respect to the presence of peripheral vascular disease, cerebrovascular disease, and generalized arteriosclerosis were relatively modest; the probability of these differences being due to chance ranged from one in five to one in 20. The extent of the excess risk manifested among diabetic patients, as compared with nondiabetics, was also relatively small: 33% for generalized arteriosclerosis, 23% for cerebrovascular disease, and 19% for peripheral vascular disease. The fact that these statistics were based on relatively small numbers of observations may account for this apparently minor association.

On the other hand, since the diabetics and nondiabetics compared in this analysis were well matched with regard to race, sex, age, place of occurrence, month/year of death, and since the disease information used for this analysis was reasonably complete (based on two complementing sources, death certificates and special physician questionnaires), the observed relationship of diabetes with these disease entities may in fact reflect the true relationship, at least as a cause of death. A further study is needed to substantiate this finding so as to verify the true importance of cerebrovascular disease, peripheral vascular disease, and generalized arteriosclerosis as a direct complication of diabetes and/or as a significant cause of death among diabetics. One should also be aware of the possible bias; i.e., most physicians believe that vascular disease is more likely, therefore more often recorded, in diabetic persons than in nondiabetics. The exact extent of this possible bias should be documented.

Certain combinations of various diseases and conditions were noted in many of the diabetic decedents analyzed. The results of this analysis are summarized in Table 9. The most frequent combination reported was hypertension and heart disease, which was recorded in 47% of the patients studied. This was followed by a combination of

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TABLE 9

MULTIPLE PHYSICAL CONDITIONS MENTIONED ON QUESTIONNAIRE, PENNSYLVANIA
(A RANDOM SAMPLE OF DIABETES): MAY 1968 - APRIL 1969

Combination of Conditions	Number of Patients	Percent of Total Patients [1]
Hypertension + Obesity	74	26.2
Hypertension + Heart	132	46.8
Hypertension + Renal	53	18.8
Hypertension + Heart + Obesity	68	24.1
Hypertension + Heart + Renal	53	18.8
Hypertension + Heart + Renal + Obesity	29	10.3
Obesity + Heart	103	36.5
Obesity + Renal	39	13.8
Ovesity + Heart + Renal	38	13.5

Note: [1] Total patients equals 282.

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obesity and heart disease (37%), hypertension and obesity (26%), hypertension, heart disease, and obesity (24%), hypertension and kidney disease (19%), hypertension, heart disease, and kidney disease (19%), obesity and kidney disease (14%), obesity, heart disease, and kidney disease (14%), and hypertension, heart disease, kidney disease, and obesity (10%).

In investigating the extent of the problem of multiple-cause mortality among diabetics, it is necessary to determine whether the presence of diabetes substantially reduces an individual's survivor-ship function. The best way to look at this problem is to compare the survival experience of a diabetic population with a similar popu-lation of nondiabetics. The many studies conducted with different groups of diabetics have shown, in general, that life expectancy among diabetic patients is less than that of comparable groups of nondiabetics.

Kessler (39) studied one of the largest populations of diabetics. He obtained data on 21,447 diabetic patients first seen at the Joslin Clinic in Boston from January 1930 to July 1956. All were followed to January 1, 1960. He found that for both males and females there were significantly (p .01) more deaths than predicted if the age-sex specific death rates of the standard population (population of Massachusetts) were operating. The ratio of observed to expected deaths, known as the standard mortality ratio (SMR), was 1.66 for males and 2.18 for females. The ratios were highest among men 20 to 39 years of age and women 30 to 39 years of age, reflecting a greater risk for persons who develop diabetes at earlier ages (juve-nile-onset diabetics). The SMR due to diabetes was 31.6 for males and 23.15 for females; and the SMR's for males and females with coronary heart disease were 1.53 and 2.20 respectively. Once dia-betes and coronary heart disease were removed as causes, the SMR's were 0.93 and 1.09 for males and females respectively. These SMR's, which are close to 1.00 (unity), indicate that the excessive mor-tality of the population with diabetes is due, for the most part, to diabetes and coronary heart disease.

Excessive deaths in this population were also observed for cerebro-vascular disease and respiratory tuberculosis in females and for generalized arteriosclerosis in males. Mortality from other causes did not show an increase in this population, however. Kessler's data further show that the mortality experience of diabetics vis-a-vis the general population has not improved with time.

Another study done on the Joslin Clinic population by Entmacher and others (23) looked at patients first seen by the Clinic from 1950 to 1958 and followed them through 1961. The ratio of death rates of Joslin Clinic patients to those for the entire population of New England (1949-51) was studied. For males, the ratios ranged from 1.7

to 6.9 and for females from 2.4 to 9.5. In both sexes, it appeared that the ratio peaks in the 20-39 year age groups and declines consistently after that. These data support Kessler's findings that persons who develop diabetes at an earlier age (below 40 years) have higher relative mortality than persons who are adult-onset diabetics, when compared with a nondiabetic population. These data also show that the death ratios for females are consistently higher than for males.

A study reported by Pell and D'Alonzo (70) on the survival experience of DuPont employees with diabetes showed similar results. Their study compared the ten-year survival of 370 diabetic male employees of DuPont with a series of matched controls. Subjects were matched by age, ± 5 years, and by occupation. The cumulative survival of the diabetics was consistently less than the controls. After five years, 9% of those with diabetes had died, whereas only 3.2% of the controls were dead. After ten years, the comparable figures were 25.4% for the diabetics and 9.7% for the controls. It is apparent that the discrepancy becomes larger the longer they are followed. The ratio of death rates among diabetics to that of their matched controls ranges from 1.50 to 6.74, with the largest ratio occurring among men under 45 years of age.

These data again support the hypothesis that the effects of diabetes on mortality are more severe among persons with onset at an early age. Among male employees with a history of hypertension or coronary heart disease at entry to the study, the mortality ratio of diabetics to controls is smaller (1.50) than for male employees with no such history (about 2.50). These data, therefore, suggest that in the presence of conditions related to cardiovascular disease, the additional effect of diabetes is less if these conditions do not exist. The mortality ratios are larger for coronary heart disease (2.87) and cerebrovascular accident (2.83) than for any other causes.

Garcia and others (93) used the data from the Framingham study to compare the experience of persons with diabetes to the rest of the Framingham population. Of the total 5,209 individuals in the Framingham study, 239 were diagnosed as having diabetes sometime in the first eight examinations. Using the mortality experience of the rest of the population to predict expected deaths, SMR's were computed for several causes. The overall SMR was 2.80; for coronary heart disease, including both sudden and non-sudden deaths, it was 2.95; and for cerebrovascular accident, the SMR was 4.21.

Several life insurance companies have conducted extensive studies on the survival experience of insured diabetics as compared to similar insured persons without diabetes. Goodkin and others (27) did a 20-year mortality study of diabetic patients (15 to 61 years of age)

who applied for insurance with the Equitable Life Assurance Society between 1951 and 1961, and who were followed through 1970. In general, those insured by the company represent a cross-section of the diabetic population of the United States. As compared with the overall population insured by Equitable, the SMR for diabetics was 1.67. Looking at the data by ten-year age groups, the SMR's ranged from 1.19 to 4.53. The highest ratio occurred in the group 20-29 years of age at the time of application. Since the majority of life insurance policyholders are male, these data support the results noted previously for the Joslin Clinic data. When both age at application and duration of diabetes prior to application are considered, the data indicate that the 20-29 year age group has consistently highest SMR's for each duration than all other age groups.

John W. Barch (92) did a similar study on diabetic persons insured by the Lincoln National Life Insurance Company who were issued policies between 1946 and 1965. Individuals were traced up to 1966. The ratio of observed to expected deaths ranges from 2.17 to persons 60-64 years of age at issue to 7.81 for those in the 20-29 year age group. Expected deaths were calculated, using the overall experience of the Lincoln National insured population. As in all the other studies previously discussed, the greatest number of excessive deaths occurs in the group with early onset of diabetes. The excess of deaths was due to diabetes itself in those with early onset of diabetes (an excess of 29% of deaths due to diabetes in the 20-29 year age group), and due to arteriosclerotic heart disease in older persons (an excess of 16%).

Although in all cases it is clear that the largest discrepancy between actual and expected rates occurs in individuals with onset of diabetes before age 40, the ratios from age 40 on are still close to 2.00, and become considerably higher for deaths due to cardiovascular diseases. A study (34) of 2,167 newly diagnosed diabetics over 40 years of age, first seen at the Joslin Clinic between 1957 and 1963 and followed until 1971, was recently completed. This study looked at the relative survival of these diabetics compared with that of the reference population of Massachusetts. Relative survival is the ratio of the observed survival rates to those expected if the age-sex specific death rates for the reference group were operating. The relative survival after ten years for persons controlled by some form of medication ranged from 50% to 90% for all causes of death and 40% to 85% for deaths due to coronary artery disease. These Joslin Clinic data indicate that there is a decreased survival experience as compared with a similar population of nondiabetics. The excessive mortality is especially apparent for cardiovascular causes.

7. STATISTICAL MODELS

Perhaps the most important but difficult problem that needs to be addressed in diabetes mortality is that of developing an acceptable statistical model capable of quantifying the relative contribution to death of all the coexisting conditions considered to be caused by diabetes, but usually not specified as such on death certificates. Is it possible to develop such a model?

To answer this question, one should consider the population of diabetic persons who have died in the United States. However, the current coding of death certificates does not permit identification of all diabetic decedents. Diabetes is mentioned only in those cases where it is thought to have contributed, in some way, to the event of death. Therefore, analysis can be done only on this identified portion of diabetic deaths. If the experience in Pennsylvania (80) may be generalized, about 10% of the diabetic deaths will be missing. Using the available population of deaths, it is possible to postulate a statistical model to describe the relationship of various underlying causes to contributory conditions. To do so, it is necessary to define C_D as the underlying cause of death (e.g., diabetes, ischemic heart disease, hypertension, etc.), and X_1, X_2, ..., X_k as k other conditions in which we are interested.

Now define the following probabilities:

Equation 1. $P(C_D = X_D \mid$ no other conditions) as the probability that the underlying cause of death is equal to X_D when no other conditions are present.

Equation 2. $P(C_D = X_D \mid X_i)$ as the probability that the underlying cause of death is X_D given condition X_i (e.g., coronary heart disease) is also present.

Equation 3. $P(C_D = X_D \mid X_i$ and no other conditions) as the probability that the underlying cause of death is X_D given that only condition X_i is present. This differs from (2) above in that (2) does not exclude the presence of other conditions.

Equation 4. $P(C_D = X_D \mid X_i$ and X_j and no other conditions) as the probability that the underlying cause of death is X_D when only conditions X_i and X_j are present. Similar probabilities may be defined for all combinations of other conditions.

For any cause X_D (diabetes, coronary heart disease, etc.), consider:

Equation 5. $P(C_D = X_D \mid X_i$ and no others$) - P(C_D = X_D \mid$ no others$)$
as a measure of the deaths from cause X_D attributable
to condition X_i;

and

Equation 6. $$\frac{P(C_D = X_D \mid X_i \text{ and no others})}{P(C_D = X_D \mid \text{no other conditions})}$$

as a measure of the "relative risk" of death from
cause X_D when condition X_i is also present.   By
looking at the various combinations of conditions,
it is possible to evaluate the attributable and
relative risk of death from cause X_D when these con-
ditions are present vs. when they are not or when
only some subset of them is present.

The present state of the multiple cause data (in terms of what has
been analyzed and what is available) does not allow estimation of these
probabilities.   To do this, it would be first necessary to decide how
many specific conditions (causes of death and coexisting conditions)
are to be considered.   Finally, the multiple cause data would have to
be tabulated as follows:

UNDERLYING CAUSE	OTHER CONDITIONS LISTED	NUMBER OF DEATHS
A	ALONE	
A	B only	
A	C only	
A	B & C only	
A	D only	
A	B & D only	
A	C & D only	
A	B, C, & D only	

etc. for all combinations of conditions.

Using this method of classifying the data, the probability

$$P(C_D = X_D \mid X_i \text{ alone}) \text{ would be estimated by}$$

$$\frac{\text{No. of deaths due to } X_D \text{ where only condition } X_i \text{ is present}}{\text{Total No. of deaths where only condition } X_i \text{ is mentioned and } X_i \text{ is not underlying cause}}$$

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Similarly,

$$P(C_D = X_D \mid X_i \ \& \ X_j \text{ alone}) \text{ would be estimated by}$$

No. of deaths due to X_D where both conditions X_i & X_j and no
others are present
_____
Total No. of deaths where both conditions X_i & X_j and no others
are mentioned and neither is underlying

An automated method of obtaining these quantities could be worked
out without too much difficulty. For purposes of complete analysis,
the multiple cause data should be tabulated by age and sex.

Our next effort should be directed toward constructing a statisti-
cal model where certain specific conditions (considered to be caused by
diabetes) such as renal disease, ischemic heart disease, etc., may be
given appropriate scores or relative measures as to their contribution
to death among persons with diabetes.

To properly develop a model to evaluate the association of various
factors with diabetes, one would need a population of diabetics (not
all dead) that were to be followed until death or for some relatively
long period of time. At the time of entry to the study, one would need
to collect information about the state of diabetes, e.g., years since
onset, age at onset, treatment, and type of control (blood glucose),
as well as information about various associated conditions of interest
such as history of ischemic heart disease, cerebrovascular accidents,
hypertension, renal disease, retinopathy, etc. During the follow-up
of these individuals, both mortality (by cause) and morbidity (con-
ditions mentioned above) should be obtained. It would then be possi-
ble to use some of the standard models for predicting mortality (and
morbidity) with covariates. The simplest model, popularized by the
analysis of the Framingham data, is the multiple logistic model (94).
Using this model, one can estimate, for example, the probability of
dying from cause X_D or of having a nonfatal occurrence of X_D in a
period of R years. This probability is

Equation 7. $$P = \frac{1}{1 - e^{-(a + b_1 y_1 + b_2 y_2 + \ldots + b_s y_s)}}$$

where y_1, y_2, ... y_3 represent (a) factors associated
with diabetes at entry to the study and (b) conditions
present at entry. The coefficients b_i's represent the
contribution of a condition (or factor) y_i to the
event of interest in this diabetic population. These
coefficients have standard errors (SE_{b_i}) associated

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with them, and $Z_i = \dfrac{b_i}{SE_{b_i}}$, which corrects for dif-

ferences in measurement scales, may be thought of as the relative contribution of factor y_i to the event being evaluated. There are standard programs available to estimate the b_i's from data and these survival functions may be evaluated for every year of follow-up or for the experience of five or ten years or whatever intervals are convenient.

To accurately compare the effect of certain conditions -- e.g., iso-chemic heart disease -- on survival between diabetic patients and the rest of the population, it would be necessary to fit such a model to a similar group of nondiabetics as well. The data from the Framingham study would provide an initial opportunity to do this. However, there has been no attempt to fit a logistic model to the diabetic portion of the population and to compare the parameters of this group with those fitted for the nondiabetic portion of the population.

In summary, the fitting of these models to a diabetic population will provide an estimate of the relative contribution of several factors to a particular event of interest. Comparison of the relative contribu-tions in the diabetic group with those in a similar group of non-diabetics will give an estimate of how the relative effects of the factors change in the presence of diabetes.

Since such a study would take a considerable amount of time, one could attempt an initial estimate of this by looking at deaths due to cause X_D in persons with diabetes listed on the death certificate vs. those with no diabetes listed.

For purposes of this study, redefine $\hat{P}$ as the probability that the cause of death is X_D, and define P as before (Equation 7), but now $y_1, \ldots, y_s$ represent all other conditions listed on the death certificate. It is possible to calculate the ratio of coefficients to their standard errors for both diabetic and nondiabetic deaths and compare the relative contribution y_1 in both groups. One could easily control the age and sex in this analysis by including age and sex as factors, or alternatively, by stratifying by age and sex. If the multiple cause mortality data were organized as described pre-viously for diabetic and nondiabetic deaths, such a model could be constructed for each cause of death.

D. SUMMARY AND CONCLUSIONS

After steadily increasing in importance as a cause of death since the turn of the century, diabetes mellitus now ranks as the fifth leading underlying cause by disease in the United States.

However, this ranking position given to diabetes among major causes of death is grossly misleading. It should be recognized that a large number of diabetic patients die from its complications, mostly vascular pathologies; yet these patients are usually not counted as having died of diabetes under the existing mortality reporting system. In addition, approximately 10% of the time, diabetes is not even recorded on death certificates according to the current rules of certifying causes of death.

This poor visibility, primarily attributed to the existing method of disease classification and to the selection of underlying cause of death, has led to an undue underestimation of the complex and sig-nificant health problems which diabetes poses. Consequently, medical research and social action programs related to diabetes have not been supported at a level commensurate with its true importance as a major medical and health problem. In fact, since the advent of insulin, there have been no major breakthroughs either in the primary or secondary prevention of diabetes.

A recent study conducted in Pennsylvania clearly indicates the basic magnitude of the underestimation of diabetes mortality. Specifically, if only the underlying cause is considered, as is conventionally practiced, the diabetes death rate for 1969 was 22 per 100,000 population in Pennsylvania. If the contributory and underlying causes were considered together, the rate would rise to 150 per 100,000. If the number of unrecorded diabetics was added to that of all recorded diabetics, the overall diabetes death rate would reach as high as 161 per 100,000. If these statistics were applied to the total U.S. population, nearly 304,000 people, rather than 38,000 as officially reported, would be expected to die annually with diabetes in the United States. In other words, if all recorded and unrecorded diabetics on death certificates were counted together, diabetes could well be considered the third leading cause of death.

Another difficult problem associated with diabetes is that of delineating so-called "diabetic complications" which encompass a vast range of vascular pathologies, many of which -- particularly small vessel complications -- are not even mentioned on many death certifi-cates. It is essential to develop some equitable methods of deter-mining which of the many significant vascular and other complications may be considered as having been caused by diabetes. Such methods must be capable of dealing with population data so that the results

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can be applied to estimating the relative contribution of diabetes to each of the other major diseases which are in fact reported as the underlying cause of death. Such data, in turn, would be useful for estimating the true economic and social impacts of diabetes.

Since diabetes is a common chronic disease affecting all ages including infants and young children, particularly the juvenile-onset type which is far more serious in medical complications than the adult-onset type, the potential benefit of an effective diabetes control program would be much greater than that of other chronic disease programs in which only adult populations may be affected. Yet, age at first diagnosis is not usually recorded on death certificates; therefore, death certificates do not provide any useful means for distinguishing these two different types of diabetes, nor can they be used for determining the survival function of diabetic patients of the different types. Furthermore, there is some systematic bias in recording the residence of the deceased on death certificates, with relatively more deaths being allocated to urban areas than there should be. This biased mortality reporting practice has caused some possibly inapt assessment of the existing diabetes problems between rural and urban areas.

Since mortality statistics are essentially based on data from death certificates which are prepared, in part, by physicians, these problems originate in the physician's knowledge of his patient's medical history and his understanding of the rules of death certification, particularly with respect to selecting diabetes as the underlying cause or as a contributory cause.

The major goals of our future efforts in dealing with the problems of diabetes are (1) to improve visibility of this disease as a leading cause of death among all major causes of death by disease, and (2) to develop a better understanding of the nature and extent of "diabetic complications" as reflected in morbidity and mortality statistics. To achieve these goals, several different approaches may be employed, some affording immediate action and others requiring further study and research for future projects. Diabetes' visibility can be improved by recording diabetes on all death certificates when this disease is present in the individual regardless of its relationship to his death, and by systematic analysis and reporting of multiple causes of death particularly when diabetes is involved. This will require an organized and extensive training program directed toward medical students and postgraduate physicians who certify causes of death. "Physician's Handbook on Medical Certification: Death, Fetal Death, Birth" should be modified to meet these requirements.

Concurrently, a new classification of diseases is needed, such as "combination coding," particularly when diabetes is involved, and an

improved method of selecting diabetes, among other competing causes, as the underlying cause of death is also mandatory. This change will require the cooperation of the World Health Organization and is feasible only when the International Classification of Diseases is revised (every ten years). Special studies may be conducted on a smaller scale to demonstrate its feasibility before nationwide implementation is attempted.

Feasibility studies should be conducted to determine whether age at first diagnosis of diabetes can be systematically recorded on death certificates. Should this be possible, such data would be useful for evaluating the natural history of the two different types of diabetes, juvenile-onset and adult-onset. Furthermore, valid data on multiple causes of death will make it possible to determine the survival function of diabetic patients with complications, as compared with those without complications or with nondiabetics. Follow-back surveys will be needed to obtain supplemental information of a medical, demographic, and socioeconomic nature useful for control and research purposes.

E. FUTURE DIRECTIONS

1. GOAL

To improve visibility of diabetes mellitus as a leading cause of death among all major causes of death by disease; to develop a better understanding of the nature of "diabetic complications"; and to determine the more exact magnitude of such complications which affect life expectancy, so that future funding for diabetes programs may be improved substantially.

2. SPECIFIC OBJECTIVES

For achieving the above goal, a number of specific objectives may be formulated within two general categories: one, short-term for immediate action; and the other, long-term for research and development for future action.

a. Short-Term Objectives:

1) To institute a new practice of recording diabetes on death certificates for all those who have diagnosed diabetes at the time of death regardless of its relationship to death. This would give a more accurate basis for estimating the prevalence of diabetes in the population.

2) To develop a program of medical and postgraduate medical training designed to improve physicians' understanding and technique of how to select and certify multiple causes of death, particularly when diabetes is present. "Physician's Handbook" should be revised, specifically with respect to dealing with diabetes.

3) To improve accuracy of residence allocation on death certificates with regard to city, borough, or township. "Funeral Director's Handbook" should be revised to reflect this emphasis, and a program of training seminars should be instituted for funeral directors on how to fill out sociodemographic data on death certificates, particularly with respect to residence.

4) To develop and standardize a multiple-cause reporting system (ACME) so that diabetes can be identified and evaluated either singly or in combination with other competing causes of death.

b. Long-Term Objectives:

1) To study and determine more equitable criteria and methods
   of classifying (single condition or combination of related
   conditions) and selecting (underlying versus contributory)
   diabetes as cause of death.

2) To study and evaluate the feasibility of recording "age
   at first diagnosis of diabetes" on death certificates;
   this information, if recorded systematically, would be
   useful for distinguishing the two types of diabetes,
   juvenile-onset and adult-onset.

3) To study and develop an empirical biometric model to
   delineate the relative contribution (risk) of diabetes
   in competition with other major causes of death by disease.
   If constructed, such a model would be useful in upgrading
   the "visibility" of diabetes in the overall ranking among
   all leading causes of death in the United States.

4) To study and assess reasons why the diabetes death rate
   in the old age groups is rising sharply in recent years.
   Is it a reflection of the aging process in the population,
   the method of treatment, and/or changes in the configura-
   tion of other causes of death?

5) To study and calculate differential "survival functions"
   of diabetic persons as compared with nondiabetics, and
   diabetics without complications as compared with diabetics
   with complications.

6) To obtain from NCHS a computer tape of the 1968 data,
   hire a programmer, and provide computer funds for a com-
   plete analysis of the multiple cause data by age, sex,
   and specific combinations of coexisting conditions.

7) To use the 1968 national data on multiple causes of death
   to fit the logistic model to diabetic and nondiabetic
   deaths in order to determine the relative contribution
   of various coexisting conditions on deaths from specific
   causes.

8) To obtain from the Framingham data an analysis by risk
   factors for specific diseases and to compare the rela-
   tive contribution of these factors among diabetics
   versus the rest of the Framingham population.

9) Once objectives 6 and 7 are completed for 1968 data and have been shown to work, it is further recommended to obtain copies of the 1969, 1970, 1971, 1972, 1973, and 1974 computer tapes containing multiple causes of death for more complete analysis and evaluation.

3. APPROACHES

Several different approaches may be used to accomplish the stated specific objectives, depending upon the nature of the problems presented.

a. Survey and Research:

For those problems for which only limited knowledge and understanding exist at present, further in-depth survey or research would be needed.

b. Demonstration:

For those problems which are reasonably well understood, but lack specific information for an immediate action, an experimental or demonstration project may be considered.

c. Education and Training:

For those problems which require essentially teaching efforts to remedy, a series of educational and training programs may be instituted.

4. PROJECTS

a. Death Certificate Linkage Study

b. The Use of Death Certificates in Obtaining Supplementary Information on Selected Diagnosed Disease

c. Medical and Postgraduate Training on Death Certificates

d. Comparison of Residence on Death Certificates with Actual Place of Residence at Time of Death

e. Multiple Cause of Death Statistics

f. Nationwide Multiple Cause of Death Classification System

g. Problems in Classifying and Selecting Diabetes as a Cause
    of Death

h. Recording "Age at First Diagnosis of Diabetes" on Death
    Certificates

i. Biometric Model to Delineate Relative Contribution of Diabetes
    in Competition with Other Major Diseases

j. Assessment of Rising Diabetes Mortality in Old Ages

5. PROJECT SUMMARY SHEETS

PROJECT SUMMARY SHEET

PROJECT TITLE: DEATH CERTIFICATE LINKAGE STUDY

OBJECTIVE: Develop a system which will allow efficient inter-
                 relating of death certificate information with other
                 local, state, and federal data to meet specific needs.

APPROACH TITLE:

    Link death certificate data with data collected by agencies such
    as the Bureau of Census and National Center for Health Statistics.

DESCRIPTION OF PROJECT:

    The feasibility and utility of linked records will be investigated
    in this project.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Provision of funds and personnel.
    2. Availability of data constrained to confidentiality.
    3. Assignment of identifying characteristics.
    4. Ensuring of confidentiality of linked data.

PRESENT STATUS:

    The Bureau of Census has researched the possibility of linking
    census and vital statistics data.

INPUT REQUIRED:

    Considerable input is required in terms of both manpower and
    funds.

PROJECT SUMMARY SHEET

PROJECT TITLE: THE USE OF DEATH CERTIFICATES IN OBTAINING SUPPLE-
                  MENTARY INFORMATION ON SELECTED DIAGNOSED DISEASE

OBJECTIVE: Determine the feasibility of routinely recording
                  selected diagnosed diseases on death certificates
                  (or an attachment).

APPROACH TITLE:

    Recording diabetes on death certificates for all decedents
    who have diagnosed diabetes at the time of death.

DESCRIPTION OF PROJECT:

    This would be a one-year demonstration project conducted in
    selected states.

PRESENT STATUS:

    Death certificates have not been used for this purpose in the past.

INPUT REQUIRED:

    Cooperation of states and certifying physicians.

FORM OF RESULTS:

    Results will be published.

PROJECT SUMMARY SHEET

PROJECT TITLE: MEDICAL AND POSTGRADUATE TRAINING ON DEATH CERTIFICATES

OBJECTIVE: Obtain accurate and complete cause of death certifi-
                 cation on death certificates.

DESCRIPTION OF PROJECT:

    This will be a two-year educational project in which all Medical
    and Osteopathic Medical Schools and hospitals in the United States
    will participate.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1.   Funding.
    2.   Cooperation of medical schools.
    3.   Cooperation of hospitals.

PRESENT STATUS:

    Physicians presently receive little formal instruction concerning
    medical certification of causes of death.

INPUT REQUIRED:

    Special instruction and course work at the university level by
    knowledgeable individuals. Educational programs involving lec-
    tures, films, etc. at the hospital level. Provision of
    "Physician's Handbook" to all practicing physicians.

PROJECT SUMMARY SHEET

PROJECT TITLE: COMPARISON OF RESIDENCE ON DEATH CERTIFICATES WITH
                 ACTUAL PLACE OF RESIDENCE AT TIME OF DEATH

OBJECTIVE: Determine the magnitude of the problem resulting from
                 errors in residence allocations in death certificates.

APPROACH TITLE:

   Study of residence reporting and allocation on death certificates.

DESCRIPTION OF PROJECT:

   Selected states will participate in this one-year survey-research
   project in which the magnitude of the residence allocation problem
   will be determined.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Adequate funding.
   2. Cooperation of selected states.

PRESENT STATUS:

   It is recognized that a problem does exist, at least in certain
   states. However, the magnitude of problem in this important area
   is largely unknown.

FORM OF RESULTS:

   Published reports showing magnitude of error (or agreement) for
   selected areas of the country.

PROJECT SUMMARY SHEET

PROJECT TITLE: MULTIPLE CAUSE OF DEATH STATISTICS

OBJECTIVE: Meet the need for data on diabetes as contributory as well as underlying cause of death.

APPROACH TITLE:

The use of multiple cause of death data in developing underlying and contributory cause of death statistics.

DESCRIPTION OF PROJECT:

The role of diabetes as a cause of death is not delineated by official underlying cause of death statistics.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

1. Availability of sufficient resources at the National Center for Health Statistics to process, tabulate, analyze, and publish data on a timely basis.
2. Provision of funds and technical assistance to individual states for use in developing multiple cause of death systems.

PRESENT STATUS:

The National Center for Health Statistics has utilized multiple cause of death coding since 1968; however, very little information is available because sufficient resources have not been available to analyze and publish the data.

INPUT REQUIRED:

Existing death certificates can be used, but additional personnel and funds will be required to produce desired results.

FORM OF RESULTS:

Publications and computer tapes containing more complete data on diabetes and other diseases.

PROJECT SUMMARY SHEET

PROJECT TITLE: NATIONWIDE MULTIPLE CAUSE OF DEATH CLASSIFICATION
                  SYSTEM

OBJECTIVE: Implement a nationwide system for the Automated
                  Classification of Medical Entries (ACME) capable of
                  producing multiple cause of death data for all geo-
                  graphic levels.

DESCRIPTION OF PROJECT:

    Funding and technical support will be made available to approved
    states for the development and implementation of Automated
    Classification of Medical Entities Systems.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1.   Provision of funding and other resources.
    2.   Cooperation of NCHS.

PRESENT STATUS:

    The National Center for Health Statistics has utilized the ACME
    system of coding since 1968; however, very little multiple cause
    data are available for health researchers.

FORM OF RESULTS:

    This project will enable the various states to produce the mul-
    tiple cause of death data necessary to meet their needs.

PROJECT SUMMARY SHEET

PROJECT TITLE: PROBLEMS IN CLASSIFYING AND SELECTING DIABETES AS A
                 CAUSE OF DEATH

OBJECTIVE: Investigate the existing method of disease classifi-
                 cation and selection of underlying cause of death which
                 may have resulted in an undue underestimation of the
                 complex and significant health problems which diabetes
                 poses.

APPROACH TITLE:

    Equitable criteria and methods of classifying and selecting dia-
    betes as a cause of death.

DESCRIPTION OF PROJECT:

    This one-year research project will investigate the impact of the
    existing classification of disease scheme on the selection of
    diabetes as a cause of death.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Availability of personnel and resources.

PRESENT STATUS:

    This problem has never been researched.

FORM OF RESULTS:

    Results will be published and, if warranted, recommendations made to
    revise the existing system of classifying diabetes as a cause of
    death.

PROJECT SUMMARY SHEET

PROJECT TITLE: RECORDING "AGE AT FIRST DIAGNOSIS OF DIABETES" ON
                 DEATH CERTIFICATE

OBJECTIVE: Determine the feasibility of systematically recording
                 age at first diagnosis of diabetes on death certificate.

DESCRIPTION OF PROJECT:

    This one-year demonstration project conducted in selected states
    would provide data useful for evaluating the natural history of
    two different types of diabetes, juvenile-onset and adult-onset.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Personnel and other resources.
    2. Cooperation of selected states.

PRESENT STATUS:

    Provision is made on death certificates to record interval between
    onset of disease and death. The quality of this information, how-
    ever, is suspect.

INPUT REQUIRED:

    Certifying physicians.

FORM OF RESULTS:

    Results will be published.

PROJECT SUMMARY SHEET

PROJECT TITLE: BIOMETRIC MODEL TO DELINEATE RELATIVE CONTRIBUTION
OF DIABETES IN COMPETITION WITH OTHER MAJOR DISEASES

OBJECTIVE: To develop an acceptable statistical model which is
capable of quantifying the relative contribution to
death of all coexisting conditions considered to be
caused by diabetes but not usually specified as such
on death certificates.

DESCRIPTION OF PROJECT:

Logistic models will be developed and fitted to diabetic popula-
tion to estimate the contribution of each of several factors to a
particular event of interest.

PRESENT STATUS:

There has been no attempt to fit a logistic model to the diabetic
portion of the population and to compare the parameters of this
group with those fitted to the nondiabetic portion of the
population.

FORM OF RESULTS:

Published reports on the development of the models and their
applicability for specific uses.

PROJECT SUMMARY SHEET

PROJECT TITLE: ASSESSMENT OF RISING DIABETES MORTALITY IN OLD AGES

OBJECTIVE: Determine why diabetes mortality rates for persons
                  85 years and over increased by over 50% between
                  1949 and 1967 and remain at a high level.

DESCRIPTION OF PROJECT:

    This is a one-year research project.

PRESENT STATUS:

    It is not presently known what the rising diabetes mortality rate
    among the aged is attributable to.

FORM OF RESULTS:

    Results will be published.

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G. APPENDIX

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APPENDIX: Flow of the Death Certificate from the Funeral Director and
Physician to the Eventual Publication of National Statistics.

RESPONSIBLE PERSON OR AGENCY	DEATH CERTIFICATE
Physician, Other Professional Attendant, or Hospital	1. Completes medical certification and signs certificates. 2. Returns certificate to funeral director.
Funeral Director	1. Obtains personal facts about deceased. 2. Takes certificate to physician for medical certification. 3. Delivers completed certificate to local office of district where death occurred and obtains burial permit.
Local Office (may be Local Registrar or City or County Health Department)	1. Verifies completeness and accuracy of certificate. 2. Makes copy, ledger entry, or index for local use. 3. Issues burial permit to funeral director and verifies return of permit from cemetery attendant. 4. Sends certificates to State Registrar.

City and county health departments use certificates in allocating medical
and nursing services, followups on infectious diseases, planning programs,
measuring effectiveness of services, and conducting research studies.

State Registrar, Bureau of Vital Statistics	1. Queries incomplete or inconsistent information. 2. Maintains files for permanent reference and as the source of certified copies. 3. Develops vital statistics for use in planning, evaluating, and administering State and local health activities and for research studies. 4. Compiles health related statistics for State and civil divisions of State for use of the health department and other agencies and groups interested in the fields of medical science, public health, demography, and social welfare. 5. Prepares copies of death certificates or records for transmission to the National Center for Health Statistics.
Public Health Service National Center for Health Statistics	1. Prepares and publishes national statistics of deaths and constructs the official U.S. life tables and related actuarial tables. 2. Conducts health and social-research studies based on vital records and on sampling surveys linked to records. 3. Conducts research and methodological studies in vital statistics methods including the technical, administrative, and legal aspects of vital records registration and administration. 4. Maintains a continuing technical assistance program to improve the quality and usefulness of vital statistics.

Report of the

National Commission on Diabetes

to the Congress of the United States

Volume III

REPORTS OF COMMITTEES, SUBCOMMITTEES,

AND WORKGROUPS

Part 2

SCOPE AND IMPACT OF DIABETES (II)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service   National Institutes of Health

"The National Diabetes Mellitus Research and Education Act" (Public Law 93-354), signed by the President on July 23, 1974, directed the appointment of a National Commission on Diabetes whose charge was to formulate a long-range plan of research and education to combat diabetes mellitus. The Commission submitted its report to Congress on December 10, 1975.

REPORT OF THE NATIONAL COMMISSION ON DIABETES

Report of the

National Commission on Diabetes

to the Congress of the United States

Volume III

REPORTS OF COMMITTEES, SUBCOMMITTEES,

AND WORKGROUPS

Part 2

SCOPE AND IMPACT OF DIABETES (II)

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VOLUME III

REPORT OF THE COMMITTEES,
SUBCOMMITTEES, AND WORKGROUPS

PART 2

Report of the Committee on the
Scope and Impact of Diabetes

TABLE OF CONTENTS

PART II

V. Report of the

WORKGROUP ON

MORBIDITY

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

Thaddeus E. Prout, M.D.

1

PREFACE

The subject of morbidity in a major systemic illness such as diabetes is encyclopedic. Since it is the purpose of this section to emphasize the scope of this disorder, the following subjects have been selected as illustrative of the major morbid problems associated with diabetes:

1. Microvascular disease, using ocular disease and renal disease as examples,

2. Macrovascular disease, using coronary heart disease, cerebral vascular disease, and major vessel disease as examples,

3. Neuropathy, and

4. Ketoacidosis or coma.

A.   REPORT OF WORKGROUP ON MICROVASCULAR DISEASE*

1.   STATEMENT OF THE PROBLEM: OCULAR PATHOLOGY IN DIABETIC PATIENTS

Although there is good reason to link microangiopathy in the diabetic patient with retinopathy and to consider this the most serious ocular complication of diabetes, it is well to recall that our present relatively simplistic view of diabetic microangiopathy does not necessarily explain all of the pathologic changes in the eye of the diabetic which the physician is called upon to diagnose and to treat. In order to define the scope of diabetic eye disease more completely, the most significant complications of the eye in diabetic patients are summarized in Table 1, modified from Leopold and Leiberman (1970). The original table should be consulted for basic references. No attempt will be made to discuss all items in this table completely.

As an approach to the subject of diabetic retinopathy, three other important types of ocular pathology will be dealt with briefly here: cataract formation, glaucoma, and changes in the vitreous.

a.   CATARACT FORMATION

It is generally accepted that cataracts are unduly common in juvenile diabetic patients, and Knowles and co-workers (1965) have listed frequencies ranging from 2% to 47% depending on whether the ophthalmoscope or slit lamp examination is used for examination. Cataracts in juvenile population are often of the metabolic or "snow flake" type, while those in the older population usually are of the "senile" type and similar to those of the nondiabetic. Although the prevalence of cataract in older diabetic patients has not been studied in a completely satisfactory manner, Caird and co-workers (1968) have estimated the rate of cataract extractions to be four to six times more common in known diabetics than in nondiabetic patients. In a study of 1,024 patients having their first "senile" cataract examination, 10.7% were found to have diabetes.

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* Prepared by Drs. Thaddeus E. Prout, Harvey C. Knowles, and Curtis L. Meinert.

Table 1

OCULAR DIABETES

from Leopold and Leiberman

1.0 Lids

    1.1 Increased xanthelasma
    1.2 Increased infection

2.0 Conjunctiva

    2.1 Altered ratio of arteries to veins
    2.2 Microaneurysms

3.0 Cornea

    3.1 Pigmentary deposits on posterior surface
    3.2 Folds in Descemet's membrane
    3.3 Decreased corneal sensitivity

4.0 Anterior Segment

    4.1 Increased pigmentation
    4.2 Neovascularization

5.0 Iris

    5.1 Neovascularization
    5.2 Increased incidence of ectropion ufeae
    5.3 Vacuoles in pigment epithelium
    5.4 Dispersion of pigment into aqueous
    5.5 Increased glucogen in iris

6.0 Lens

    6.1 Fluctuation in refraction
    6.2 Increase cataract-formation, juvenile and adult
    6.3 Increased incidence of subepithelial vacuoles

7.0 Ciliary Body

    7.1 Early accommodation lost
    7.2 Ocular hypotony in coma
    7.3 Increased incidence of glaucoma, all causes.
    7.4 Increased basement membrane thickening

8.0 Vitreous

    8.1 Asteroid hyalitis
    8.2 Premature detachment of vitreous
    8.3 Site of proliferative vessel growth and hemorrhage

Table 1 (Cont'd)

9.0 Retina

9.1 Specific vascular changes (including microaneurysms, hemorrhages, exudation, microthromboses and occlusions, neovascularization, arteriosclerosis, change in veins, vascularization of nerve head)
9.2 Macular edema (probably secondary to 9.1)
9.3 Detached retina (secondary to 9.1)
9.4 Increased incidence of retinal vascular occlusion
9.5 Biochemical changes with loss of pericytes, loss of Muellers cells, changes in electroretinographs, thickening basement membrane.
9.6 Lipemia retinalis

10.0 Neuropathy

10.1 Ptosis of lid
10.2 Loss of extraocular motion
10.3 Decreased corneal sensitivity
10.4 Papillary paralysis or sluggish reaction
10.5 Increased incidence of Argyll-Robinson pupils
10.6 Loss of accommodation with third nerve paralysis
10.7 Optic neuritis

11.0 Orbital Space

11.1 Increased incidence of infection, especially mucomycosis

Since it can be readily appreciated that a large number of the patients with cataract formations have diabetes or glucose intolerance, it is important that we review briefly the problem of cataract as a whole, as summarized by the National Eye Institute (1973). More than 40,000 people are blind because of cataract and over 4,400 people lost their sight in 1972 alone for this reason. An estimated 3,013,000 people in the United States have some degree of cataract, of whom 197,000 are 17 to 44 years of age. Cataract formation in the younger age group is most often related to a metabolic problem, the commonest being diabetes.

The cause for the common occurrences of cataract in diabetic patients is under intense study. In this regard, the metabolism of sorbitol and fructose is of major interest. The role of sorbitol in cataract formation has been reviewed by Galbay (1973). Sorbitol, the alcohol of glucose formed by the catalytic action of aldose reductase, is an immediate precursor of fructose. Once synthesized intercellularly, sorbitol and fructose are unable to penetrate cell membranes and act as an osmotic force to draw water into the inter-cellular space. During incubation of a rabbit lens in high glucose media, the sorbitol and water content increases linearly with time and the lens becomes freely permeable to sodium influx and potassium efflux. These shifts in fluid and electrolytes ultimately disrupt fibers and lead to cataract formations.

Of great importance is the fact that sorbitol production and cataract formation may be prevented by the addition of inhibitors of aldose reductase to incubation media. When administered orally to rats fed high galactose diets, these inhibitors delay or prevent the appearance of galactose cataracts. The relevance of these observations to human diabetics is supported by the observation that the kinetics of aldose reductase are such that the sorbitol is formed in human subjects at high blood glucose concentrations. This begins to establish a cause-effect relationship between the diabetic state and cataract formation. The further importance of this mechanism on cataract formation and the need for further study will be documented in the section on Research.

b. GLAUCOMA

Armstrong and his co-workers (1960) found that 4.8% of patients attending a diabetic clinic had primary glaucoma against 1.8% of the nondiabetic control group. Recent clinical studies by Becker (1967) have shown, among others, the following relationships between primary glaucoma and diabetes: (1) primary open angle glaucoma is more prevalent in diabetic persons than in nondiabetics, (2) positive glucose tolerance tests are more prevalent in the glaucoma population

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than in patients without glaucoma, and (3) the glaucoma population with the positive tolerance tests appears to be more susceptible to glaucomatous visual field loss than those with a negative glucose tolerance test.

As regards secondary glaucoma, it is well established that this is more common in patients with diabetic retinopathy than in the normal population. Ocular pressure changes may be affected by disbursement of the pigmented particles, recurrent hemorrhage, rubeosis iridis, and neovascularization on the lens.

Although glaucoma is one of the leading causes of blindness, it is not clear how much of such blindness can be attributed to diabetes. According to a report compiled by the National Eye Institute (1973), glaucoma has claimed the sight of more than 34,000 Americans now living and accounts for 11% of all blindness in the United States. It has been estimated that in 1972 alone, 3,100 people lost their sight because of glaucoma. Of the 797,000 people who suffer from glaucoma, 470,000 are 65 years of age and older, 268,000 are 45 to 64 years of age, and 52,000 are 17 to 44 years.

c. VITREOUS

Although the vitreous has not been accorded a primary role in diabetic ocular disorders, increasing evidence suggests that it may be of great importance. Observations by Davis (1965) of vitreous contraction clearly pointed to the importance of this event in the initiation of a vitreous hemorrhage in patients with diabetic retinopathy. So long as vitreous contraction does not occur, the new vessels and proliferative tissue spread along the internal surface of the retina; but with vitreous contraction, the new vessels are pulled forward. The tractions of the vitreous on these new vessels are an important cause of hemorrhage.

Following up on this observation by Davis, Taylor and Dobree (1970) found that contraction of vitreous was present in nearly 80% of the small group of the patients studied with proliferative disease. The mechanism of vitreous contraction has remained obscure, but it has been suggested that there may be change in the vitreal protein which may initiate this change. The implication that vitreous changes are likely to be important factors in loss of vision in patients with diabetes requires further study. It is very important that the vitreous work go forward to prevent the pathology of the vitreous being lost as a purely secondary phenomenon associated with other morphologic changes in retinal vasculature.

2. STATE OF THE ART: DIABETIC RETINOPATHY

In order to understand the importance of diabetes as it affects the eyes, it is important for us to understand the prevalence of retinopathy, including the impact on loss of productivity and the pathophysiology underlying diabetic retinopathy. A description of the present status of our methods for prevention and correction of retinopathy will appear in the report on Treatment.

a. PREVALENCE OF RETINOPATHY IN DIABETES

It is very difficult to compare reported findings of the prevalence of retinopathy, since the populations studied are undefined mixtures of patients with unspecified numbers of adult and juvenile patients. Although it is frequently stated that diabetic retinopathy was re-discovered by Ballentyne and Loewenstein (1944) in the early forties, this is not entirely correct. It was at best re-discovered, but indeed it was never really lost (Table 2). The fact remains that Wagner (1934) stated that the prevalence of retinopathy was less than 1%. Since he was reporting on patients only a decade after the discovery of insulin, there was insufficient time for diabetic retinopathy to have developed in the surviving patients with juvenile diabetes.

By 1935, Waite and Beetham reported retinal hemorrhage in 18% of a cross-section of diabetic patients, but the admixture of juveniles and adults was not accurately known. But by 1968, it could be reliably reported that 60% of patients with diabetes for more than 15 years had some evidence of diabetic retinal diseases (Burditt et al., 1968).

White stated in 1956 that 95% of the juvenile patients were found to have diabetic retinopathy if they were followed for 30 years or more. In a long-term prospective study of juvenile diabetics reported in 1971 by Knowles, a frequency of 62% retinopathy at 25 years was found. Unlike other studies, the patients comprising this group were from a total population of juvenile patients and thus can be said to be representative of the total population of juvenile diabetes.

As to the time of onset of retinopathy, one again encounters difference in the time between the known onset of the diabetes and the appearance of simple or background retinopathy consisting of puctate hemorrhages, microaneurysms, or exudates. In the adult population, over 16% of patients were found to have retinopathy at the time the diabetes was first recognized (VAPD, 1970). In juvenile patients, it was originally believed that simple retinopathy rarely had onset before 15 years of diagnosis. Improved methods of study, including fluorescein angiography, now reveal changes in the retina

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TABLE 2

LANDMARKS IN DIABETIC RETINOPATHY (from Wise, Dollery, and Henkind)

Bowman	1854	cited by Ashton
Von Jaeger	1856	dilated veins, striate extravasations and flecks of yellow or orange material
Weber	1876	review of cases of diabetic retinopathy to date
MacKenzie	1879	recognition of microaneurysms (examined by Nettleship)
Nettleship	1888	histologic description of proliferative retinopathy and of iridis
Wagner et al.	1934	prevalence of retinopathy less than 1 percent
Ballantyne and Loewenstein	1943	"re-discovery" of microaneurysms

of juvenile patients as early as five years following diagnosis. These same methods of study have revealed a much higher prevalence of diabetic retinopathy in adult patients as well.

b.   PREVALENCE OF PROLIFERATIVE RETINOPATHY

The term proliferative retinopathy will include neovascularization and/or fibrosis in addition to simple hemorrhages and exudates. Once again, the admixture in reported series is rarely stated. In juvenile diabetics with a duration of 15 to 19 years, White reported in 1959 an instance of 18% of proliferative retinopathy; with duration of diabetes of over 30 years, proliferative retinopathy was found in 59%.

Root (1959) was probably the first to note that the average duration of diabetes before the discovery of proliferative retinopathy in the age group under 20 years was 17.1 years. None of his patients developed this disorder in less than eight years. In the age group between 20 and 39, the average duration of diabetes before proliferative retinopathy was discovered to be approximately the same.

In contrast to this, in patients over 50 years of age when diabetes was discovered, proliferative retinopathy developed in less than eight years in the cases studied (Root, 1959). This may be explained either by the possibility that, in the older group, this disease is of longer duration prior to diagnosis than is true in the juvenile patient, or that age and diabetes combine to hasten the process of proliferative retinopathy in the older group. The possible contradictions between these two explanations cannot be resolved at present.

There are no studies which demonstrate any significant sex differences in the proportion of diabetics with retinopathy. The well known higher prevalence in women over 40 and the inevitability of the higher actual number of females eligible for a progressing to the degenerative complication of diabetes lead to a predominance of females among blind diabetics.

c.   PROGRESSION OF RETINOPATHY TO BLINDNESS

A number of facts have been recorded about the rate of progression of visual acuity to blindness--from various starting points, to blindness. Beginning with diabetic patients having nonproliferative retinopathy with good vision and followed for five years, Caird (1968) found that 51.5% kept good vision; 34% had impaired vision -- that is, reduction of vision to between 20/80 to 20/200; and 14.5% became legally blind with vision worse than 20/200.

In the same five-year interval beginning with individuals with impaired vision, i.e., again defined as vision between 20/80 to 20/200, 50% became blind. If reference is made only to simple visual acuity, it can also be stated that despite ophthalmologic regression of retinopathy, 13% of the eyes nevertheless showed further progressive deterioration of visual acuity.

Deckert and his co-workers (1967) had similar findings in a small group of patients with proliferative retinopathy studied for an average of six years after this condition had been detected. In that series, 50% of the patients became blind in both eyes, that is, had vision of 20/200 or less after five years. Poulsen (1953) was the first to note that the progression also varied with the location of the proliferative area, finding that eyes with pre- or peripapillary proliferation became blind in two to three years.

To summarize, this means that 7.5% of patients with good vision become impaired annually, and approximately half of these actually go blind. If one begins with impaired vision and retinopathy, this annual rate increases from 10% to 13%, or over 50% in a five-year period.

It is also clear that age is a factor in the progression to blindness. Patients under 40 have a 25% chance of going blind if their vision is impaired, whereas patients over 60 have an 83% chance of becoming blind under similar circumstances. There is also evidence that the various items which we have ordinarily listed together as "background retinopathy" may not have the same prognostic significance. Caird (1968) has noted that there is a slightly higher risk of blindness if exudates are present than if only microaneurysms are present, although for the numbers of patients studied, this was not statistically significant. This observation, however, has led Caird et al. (1968) to look at the prognostic significance of various forms of retinopathy for life. In a group of patients attending the Radcliffe Infirmary in the year 1962, patients were matched for age, sex, and year of observation into those with normal fundi, those with microaneurysms alone, and those with more advanced retinopathy. In a seven-year period, the mean annual mortality for these matched groups was as follows: normal, 2%; microaneurysms alone, 1.5%; hemorrhages and/or exudates, 11.6%; and malignant retinopathy or more rapidly advancing proliferative disease, 14.3%. This is the first substantial evidence to suggest that microaneurysms alone do not alter prognosis over that of patients with normal fundi, but more important, that the addition of exudates to the pressure of hemorrhages increases the mortality to that equal to patients with malignant retinopathy.

Other studies have confirmed the fact that survival for ten years is less than 40% for patients with malignant retinopathy. The mortality of the blind diabetic has been estimated at approximately 15%

yearly, with a mean survival time of less than five years from the onset of blindness. This is said to be about 20 times the mortality rate for diabetics without retinopathy at age 25 and over twice that at age 70. Much of this increased mortality is associated with cardiac and renal disease, and a high correlation with the presence of these two illnesses should be expected in any prospective study. It is well recognized that while diabetic retinopathy is the most specific pathological change occurring in the diabetic, it frequently reflects changes in other organ systems elsewhere in the body. A close correlation is found between the severity of retinopathy and both nephropathy and neuropathy. The increase in percentage with duration of diabetes of all of these manifestations of diabetic pathology is well established.

The fate of the other eye in patients entering the Wilmer Institute of the Johns Hopkins Hospital with blindness in one eye has also been studied by Patz and Berkow (1968). Patients having lost vision in one eye but retaining useful vision in the second eye were followed for the fate of the second eye. This study was done prior to the introduction of either hypophysectomy or photocoagulation so that in that sense it can be considered a study of "natural history." At the end of six months, only 14 of 38 patients with proliferative diabetic retinopathy retained useful vision of 20/80 or better in the remaining eye. At the end of two years, this number had been reduced to six, and at the end of five years to one. No other comparable observation has been reported.

From these studies, it can easily be seen that the importance of diabetic retinopathy in the spectrum of public health issues lies in the number of patients in the total population developing serious visual impairment as a result of diabetes. Since the reporting of blindness is not compulsory in the United States and many blind people go without medical care, there is no way to establish with certainty the prevalence of blindness for all causes in the total population, nor is there certainty as to the exact cause of blindness in many individuals who have been reported. Even if the cause of blindness is stated, as for example glaucoma, the contribution of diabetes to the development of glaucoma may be missed, as noted previously.

In one recent report of the National Society for the Prevention of Blindness, it was estimated that almost 5,000 persons became blind from diabetes during a single year. This presumably takes into account the contributions of diabetes to senile degeneration, vascular disease, glaucoma, and other causes which are not clearly separated. Some of the information summarized by the National Eye Institute (1973) on retinal diseases may help to clarify this issue. Grouping all retinal diseases together, it was noted in that review that conditions affecting the retina are the leading cause of blindness

in the United States, accounting for 25% of all blindness in the country. A minimum of 76,500 people are blind from retinal disease, and not including the thousands of individuals who suffer disability from retinal diseases but are not legally blind. In 1972, an estimated 8,800 people became blind from retinal disease, making it the leading cause of new blindness (29.7%) that year. Diabetes is the largest single contributor to blindness from retinal causes. Of the total number of people blind from retinal disease, at least 14,400 are clearly related to the presence of diabetes. In other terms, 12.7% of first additions to registration for blindness by affection and etiology for the Model Reporting Area (1970) were attributed to diabetes, although only "retinal affections" and "multiple affections" were used to account for this percentage. Since it has already been noted that diabetes is a major contributor to both glaucoma and cataract and to retinal degeneration, it is reasonable to state that ocular disease due to diabetes may well be found to be the leading cause of blindness when all causes, direct and contributory, are taken into account.

On the basis of known facts, the following general conclusions can be drawn concerning diabetes and vision:

1) Diabetic retinopathy accounts for at least 12% of new causes of blindness added yearly, and the other three common causes of blindness such as maculopathies, lenticular problems, and glaucoma each have diabetes as a major contributor.

2) Blindness is estimated to be 25 times more prevalent in diabetics than in the general population.

3) Blindness from diabetic retinopathy occurs at a younger age than blindness from other causes. Since it is the leading systemic illness causing blindness, diabetes is, therefore, the cause of blindness many researchers would most hope to prevent by appropriate therapeutic means.

4) As one moves into the productive years, diabetic retinopathy is the most common cause of newly-reported blindness in the 41-to-60 age group, and a second most common cause in the 21-to-40 age group, second only to congenital defects.

5) Diabetic retinopathy is a relatively specific marker for this illness and, as a consequence, its prevalence or conversely its prevention -- easily quantified by noninvasive means -- is clearly the research area "most likely to succeed" in determining the efficacy of various methods of intervention.

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A predictor of both microvascular and macrovascular disease, diabetic retinopathy may well be also a predictor of mortality in the diabetic population.

d. PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

If we are to combat diabetic retinopathy effectively, we must learn much more than we now know about its pathophysiology. Many of the investigators in this field will likely have an opportunity to describe their own experimental findings for this report. The remarks here will serve primarily as an introduction and overview attempting to differentiate between well-established observation and observations still in need of further examination. Information on the epidemiology of diabetic retinopathy has been recorded in an earlier section.

There are few disagreements with the description of the normal anatomy of the retinal capillaries. Briefly, the capillaries of the normal human retina are uniform tubes four to ten microns in diameter, the walls of which are formed by a single layer of endothelial cells, underlying which is a basement membrane which splits at intervals to enclose an intramural pericyte or mural cell.

The mural cell lies within the capillary basement membrane. Found also in other extraretinal locations, it is not peculiar to the retina, although this observation was debated until quite recently. In normal human capillaries, the mural cell and the endothelial cell are present in a one-to-one ratio up until the age of about 40, with some deterioration of both the mural cell and the endothelial cell with age. The function of the endothelial cell is to form the capillary wall, but the function of the mural cell is largely unknown. Its branching cytoplasmic processes suggest that it has a contractile property or regulatory function, perhaps regulating the tone or support of the capillary, but this is largely unproven.

The first morphologic change in the eye of the diabetic person seems to be the selective loss of mural cell from the capillary wall with a decrease in mural cell to endothelial cell ratio.

Subsequent additional loss of endothelial cells leaves a network of acellular and collapsed capillaries whose work is taken over by enlarged well endothelialized channels, the so-called "shunt vessels." The original impression that these represented a microvascular "steal" by which blood was siphoned off into the larger vessels -- causing failure of profusion of the capillary bed -- has been largely superseded by the view that the shunt vessels have arisen out of necessity because

of degradation of capillary integrity. They then become the channels by which blood circulates between the arteriolar and venular side, but contribute very little if any oxygen to supply the needs of the retinal area they traverse.

An important observation has been made by Krohner and her associates (1967) that these are unlikely to be true arteriolar venular shunts under arteriolar pressure since, if anything, flow is less rapid in these larger vessels than it is through normal capillaries.

The loss of the mural cell has been suggested as an important factor in the formation of the microaneurysms causing sacculation of the unsupported endothelial tube. But aneurysms are also prominent in areas without loss of mural cells. DeOliveria (1966) found no correlation between the loss of mural cells and the sites of the microaneurysms.

It had previously been thought that new vessel formation arose only in response to the presence of previous hemorrhage. That is to say, a common cause for a neovascularization was the development and rupture of microaneurysms followed by new vessel formation in the area of hemorrhage. It is now quite clear that new vessels such as those which grow into the vitreous from the nerve head characteristically do not arise as a result of previous hemorrhage or other retinal vessel pathology, and there is frequently little or no relationship between the formation of new vessels and old retinal pathology. New vessels frequently appear de novo from the optic disc in the absence of hemorrhage or wide areas of destruction of retinal tissue elsewhere.

In addition, it should be noted that these new vessels are virtually devoid of mural cells, yet they do not have microaneurysms. This observation does not support the thesis that loss of mural cells is the principal morphologic change initiating significant retinopathy, or indeed, that it is the cause of the formation of saccular aneurysms. It seems more likely now that the biochemical stimulus for new vessel formation is related to anoxia either directly (oxygen transport) or more likely indirectly (electron transfer) as the stimulus for cell proliferation. This cellular proliferation may take the form either of endothelial overgrowth, as is frequently seen in shunt vessels and microaneurysms, or as new vessels in which endothelial cells proliferate in a more purposeful form to produce a new channel to carry oxygen to anoxic areas.

Before morphologic changes in the vessels such as aneurysms or neovascularizations occur, undoubtedly other subtle and significant biochemical changes are also taking place. The most obvious of these are changes leading to membrane thickening, as described by Siperstein, Unger, and Madison (1968), and by Kelo, Vogler, and Williamson (1972).

Briefly stated, small vessel disease in diabetics has been related to the accumulation of PAS stainable material in vessel walls, to endothelial proliferation, and to basement membrane thickening. Muscle capillary basement membrane thickness, and, by implication, changes in other small vessels less easily obtained for study appear to increase with the known duration of the diabetic state. Verification of a concomitant biochemical change in association with membrane thickening is shown in the work of Spiro and Spiro (1971). They reported that the production of hydroxylysine-linked disaccharides in the renal basement membrane of the kidney is dependent on the presence of elevated levels of glucosyl-transference regularly found in diabetic animals unless they are normalized with insulin therapy early in the course of the diabetes. Similar elevations of hydroxylysine are found in glomerular lesions of human diabetics in contrast to normal controls. It is difficult to be certain whether these changes are primary or secondary changes, nor is it yet possible to determine morphologically which is the most significant primary change taking place; but these changes are clearly important leads to future study.

For the next level of review, it is necessary to leave morphologic examination and to focus on possible stimuli for these changes. A great number of theories have been brought to bear, only some of which have proven to be useful. The suggestion that excessive amounts of human growth hormone might be a causative factor in diabetic retinopathy is supported by a number of studies. The serendipitous finding by Poulson (1953) of a regression of diabetic retinopathy in a patient who had loss of pituitary function as a result of a postpartum hemorrhage was the first stimulus to the idea that a reduction in pituitary function might be beneficial in treatment of diabetic retinopathy. This led to rather widespread use of total surgical hypohysectomy for treatment of this disorder during the past two decades. This has been reviewed by Caird (1968).

The variable course of diabetic retinopathy does not allow one to draw a conclusion as to the usefulness of this procedure in a practical sense, but it focuses on the question of whether or not there is a biochemical stimulus in the normal pituitary or the pituitary of a diabetic subject which leads to proliferative retinopathy. Although we have some evidence in many patients showing gross correlations between a fall in human growth hormone and improvement in retinopathy, there are nevertheless too many exceptions to this generalization to make the human growth hormone a comfortable unifying concept in the pathogenesis of diabetic retinopathy. Recently information from a different source has again tended to support the human growth hormone concept, though. Microangiopathic lesions have been found to be

lacking in diabetic individuals that are deficient in growth hormone, but further work in this relationship between human growth hormone and diabetic pathology is needed (Merimee, 1973).

Recent work on other hormonal influence -- notably glycagon and sommatostatin -- is challenging the concept that insulin deficiency is the sole or even the most important hormonal imbalance, in acute complications such as ketoacidosis. The role of these and other hormones in chronic complications clearly requires additional study.

Biochemical analysis, previously mentioned, emphasizes the importance of the polyol pathway in reference to diabetic pathology (Gabbay, 1973). In this regard, it is important to note that diabetic retinopathy does not develop quickly in the juvenile patient despite long periods of poor control, and it is difficult at the moment to translate findings from the biochemical laboratory directly into common observations in clinical medicine with confidence.

In the laboratories at the Johns Hopkins Hospital, a protein has been isolated which is present in the fetus when new vessel formation is an intrinsic part of the developmental process (Patz, 1975). The protein can be isolated in animals in whom retrolental fibroplasia has been created through manipulation of oxygen and has been found to reappear in the eyes of diabetic animals who are beginning to get diabetic retinopathy. This observation may point directly or indirectly to a biochemical signal which leads vessels to begin proliferation of their cells to produce neovascularization.

Vracko and Benditt (1974) have suggested that cell proliferation is a result of an accelerated rate of cell death and cell replenishment, which are viewed simply as degenerative changes. There is some evidence to suggest that there might be a defective somatic cell in patients with diabetes which renders them excessively susceptible to injury and dying.

In all of this, it is important to recall that the retina shares with other tissues of neural origin the fact that it is not insulin sensitive; and it not only accumulates glucose in the absence of insulin, as for example in the retina of the alloxan diabetic rat, but it synthesizes glycogen as well. It is not known precisely where in the retina glycogen is stored. There is no evidence of glycogen accumulation in the human diabetic retina before other pathologic changes are visible, however, although there is early glycogen accumulation in the human diabetic iris.

Among others, Ashton (1963) has suggested that the solution to the problem of the pathogenesis of diabetic retinopathy may well lie in a re-evaluation of conditions giving rise to lesions similar to those

seen in diabetic retinopathy and that this may well lead to a better understanding of aneurysms and hemorrhage as well as of new vessel proliferation.

There are some similarities between changes seen in diabetic retinopathy and those of hypertension, retinal vein thrombosis, Eales disease, macroglobulinemia, multiple myeloma, pulselessness disease, sickle cell disease, and experimental forms of anoxia. A common thread among those abnormalities has not yet been found, but certain similarities and differences should not be overlooked. Aneurysms in patients with macroglobulinemia tend to be more commonly situated in the periphery than in the posterior pole. Taylor and Dobree (1970) have carefully mapped the presence of aneurysms in relation to specific retinal areas in diabetic retinopathy, and Goldberg (1971) has found very similar findings in patients with sickle cell disease. Neovascularization has been produced experimentally following various forms of 'anoxia.' The best known of these and the state most clearly imitative of diabetic retinopathy is the neovascularization of retrolental fibroplasia of kittens described by Patz (1968). New vessels have also proliferated after retinal artery injection of fine glass particles and intravitual injections of lactic acid.

e. CORRELATION OF RETINOPATHY TO CLINICAL FEATURES OF DIABETES

Clinical observations attempting to correlate the relationship of diabetic retinopathy to other factors occurring simultaneously in diabetic patients must also be thoroughly reviewed.

1) GLUCOSE CONTROL

Of first practical importance is the question of the relation between retinopathy and glucose control in the diabetic. Unfortunately, there is little at present in the world literature on which to base judgment. Caird stated in 1969 that "the only possible solution lies in a prospective study of two groups of patients, one subjected to as close control of the diabetes as is possible and the other left untreated or only treated to relieve the immediate symptoms of diabetes. If such a study were ethically justified and could be carried out, it would still need a minimum of ten years or so to complete." This lack of information still continues.

Retrospective review of patient records does not allow one to draw any conclusions as regards the correlation between control and degenerative complications. Patients seen at the Joslin Clinic and followed

for longer than 20 years were reviewed for the presence of retinopathy (Root et al., 1954). It was found that fewer patients who have been graded as having good control had retinopathy than those graded as having poor control. Among the patients with 'good control,' 24% had severe retinopathy in contrast to 67% of patients with poor control.

By this type of review, it is not possible to rule out the highly likely possibility that both good control and lack of complication are related to the degree of metabolic deficiency. Many retrospective analyses have lacked conviction because of this fundamental unresolved question. It is essential that patients be selected and randomly allocated to groups prior to assignment of treatment if we wish to study treatment effect. If patients are stratified by control retrospectively, they may also be stratified by the degree of their biochemical defect. It should not surprise anyone to be told that the more severely ill patients have a greater amount of pathology, and little else can be gleaned from this kind of retrospective analysis.

The University Group Diabetes Program (1970) was designed to correct this error. Some information has begun to flow from this study on the clinical correlates. Of first importance is the fact that a larger number of patients than expected had diabetic retinopathy within one year of the time of the diagnosis of diabetes. It is obvious that the duration of diabetes in the adult-onset patient is virtually unknown. It was somewhat surprising, however, to find that 16% of patients in the UDGP had microhemorrhages or aneurysms in the fundi when they were carefully reviewed by fundus photography at the time of entry into the study. In addition to fundus photography, visual acuity was also followed, and an extremely preliminary observation in the placebo group indicates that there is progressive deterioration of visual acuity with time. Although less than 3% of our patients had visual acuities of less than 20/100 on admission, this increased to over 30% in ten years. It should be possible to test some of Caird's hypotheses on the role of progress of background retinopathy to blindness in this much larger population group as the data are analyzed more completely.

The contributions of clinical trials in general and the need for more detailed studies of the efficacy of present modes of therapy will be given in the section on Research. Additional therapeutic implications of the University Group Diabetic Program will be reviewed in the section on Treatment.

To pursue this correlation between glucose control and retinopathy further, an observation taken from Gerritzen's paper (1973) shows that prognosis of retinopathy over a six- to ten-year period is virtually the same in a number of groups studied despite basic differences in ethnic background, degree of control, and attention to diet. The conformity

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Table 3

PROGNOSIS FOR DIABETIC RETINOPATHY
AS REPORTED BY VARIOUS AUTHORS*

CHANGES IN RETINOPATHY IN PERCENTAGE

Author	Increase	Same		Decrease	Years of Observation
Larsson	56	27		17	10
Mikki	59	29		12	6
Inoue	53	--	47	--	10
Krall	64	--	36	--	11
Gerritzen	48	38		14	8

*(from Gerritzén, 1973)

of this data is striking. All the groups had approximately the same percentage of retinopathy which progressed, stayed the same, or regressed. It is interesting that the patient population, the severity of the diabetes, and the therapy are totally different in these widely diverse reports. Conformity of these results should be expected only if such factors as population composition, classification of the retinopathy, and present modes of treatment do not influence the spontaneous course of diabetic retinopathy (Table 3).

These data illustrate that the clinician is not yet able to alter the natural history of diabetic retinopathy by present methods of therapy. The clinician does not yet have any means by which he can return the diabetic patient to anything closely resembling the physio-logic mechanism which keeps carbohydrate, fat, and protein metabolism in the careful balance present in a normal human subject with normal endocrine function of the pancreas.

A recent observation by the King's College group (Griffith et al., 1971) showed for the first time a clear relationship between the development of retinopathy and elevations of blood glucose in a large group of patients in whom the elevation of blood glucose is not due to genetic diabetes but is secondary to hemochromotosis. In 49 patients with hemochromotosis, a number of interesting observations were made: 32 of these 49 patients had diabetes, of which 21 required insulin; of these 21, nine had evidence of retinopathy, either by clinical examination or fluorescein angiography. Of these nine, six had had diabetes for longer than ten years. It is difficult to believe that the insulin deficiency is not in some way related to the develop-ment of angiopathy in this group of patients. There is no evidence that this group of patients had a family history of diabetes. Three patients with diabetes for less than ten years also had retinopathy.

Among the patients without evidence of diabetes, two patients had retinopathy; one of these had an abnormal glucose tolerance test but was not diagnosed as diabetic. The other patient continues to raise unanswered questions, for, on the occasion of a single test, he not only had a normal glucose tolerance test but also had relatively normal levels of circulating insulin. Unfortunately, detailed blood glucose patterns over time and details as to cholesterol and triglycerides could not be given completely in this short and very provocative report.

Engerman (1975) has reported the nearly complete prevention of diabetic retinopathy in diabetic dogs treated optionally with insulin over a 10-year period, as compared with controlled diabetic dogs. This is the first reliable long-term demonstration of insulin efficacy in prevention of chronic complications in an animal model.

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All of these observations on the relation of glucose control to the development of retinopathy can be summarized to the effect that there is some evidence that, first, pure insulin deprivation leads to biochemical and/or morphologic changes in the absence of known genetic influences that are typical of diabetic complications; second, insulin may be successfully administered and retinopathy prevented in a research setting; third, the clinician has not yet arrived at an acceptable application of these principles to diabetic human subjects so as to prevent long-term complications of diabetes; and fourth, the funda-mental biochemical problems of diabetes must be studied further, along with the clinical trials of new methods of therapy in human subjects. The role of clinical trials will be reviewed briefly in the section on Research.

2) LIPIDS

In addition to glucose, metabolism interest has long been cen-tered on the effects of circulating lipids on retinopathy. Beaumont and Hollows (1972) have an interesting classification of diabetic retinopathy which they have labelled "Diabetic Lipid Retinopathy." They have stated that "our concept of this type of retinopathy is that lipolysis is so depressed that lipids accumulate in the retina as hard exudates." They further postulated that "insulin necessary to control glucose" depressed lipolysis to such an extent as to impede tissue mobilization of lipid therapy, leading to lipid accumulation in the retina. This concept, though not widely accepted, clearly points to the need for further study.

It is, of course, well recognized that clofibrate is useful in removing lipid deposits from the retina, although such deposits influence neither the presence or susceptibility to hemorrhage or exudates; nor does their removal result in return of function that is lost in association with hard exudates. It is interesting to note that hard exudates are believed to "destroy an area of retina" rather than to occur as secondary to an event which both destroys retina and leads to hard exudation. Again need for further study is obvious.

3) HYPERTENSION

The significance of hypertension and retinopathy has not been documented in a systematic fashion, particularly by means of prospective studies. Kornerup (1958) compared the blood pressure of two groups of diabetics who had had the disease for more than 15 years. A group who had no retinopathy had an average blood pressure of 128/100 mm. hg., and a second group with proliferative retinopathy had an average pressure of 141/117 mm. hg. The rise in pressure is possibly related to the

high positive correlation of diabetic nephropathy, hypertention, and retinopathy with duration of disease and may have no causal inter-relationship of any kind. On the basis of available evidence, it seems unlikely that changes in interocular pressure or systemic profusion pressure are important primary factors in the pathogenesis of diabetic retinopathy, but further study is needed.

4) DRUGS

It is entirely possible that certain medications may affect the development or progression of retinopathy (Franks, 1974). Platelet adherence and obstruction of the retinal circulation have been postulated as important contributors to diabetic retinopathy. A number of agents including aspirin and aspirin-like drugs are known to decrease platelet adhesions; whereas estrogens, naturally occurring or administered, are known to increase the likelihood of coagulation. Although some attempts have been made to discern compounding effects of these agents, they are inconclusive. Calcium dobesilate is said to reduce capillary fragility and to be useful in therapy of retinopathy. New studies are now under way to evaluate the role of viscosity in relation to diabetic retinopathy. There will be need to confirm these observations and to devise rational modes of therapeutic intervention. It is fair to say that none of these possible clues to pathogenesis of diabetic actinopathy is very convincing. Nevertheless, in view of the tremen-dous need, new directions as regards pathogenesis should be pursued simultaneously with non-invasive modes of therapy for therapeutic intervention studies.

5) OCULAR TENSION AND OPHTHALMODYNOMOMETRY

The relationship of interocular pressures to diabetic retinopathy is anything but clear. Clinical associations between diabetes and a simple glaucoma have been suggested by Armstrong and his co-workers (1960), and other observations have been made linking higher mean intraocular pressures in both young and adult diabetic patients as compared to controls. Nevertheless, because it has always been extremely difficult to eliminate bias from the patient selection in such comparisons, establishing an appropriate control population is difficult. Thus, starting with a large group of patients with adult-onset diabetes in middle life, Armaly and Baloglou (1967) demonstrated that diabetes is, if anything, associated with a reduction in ocular pressure. This observation is somewhat confirmed by population studies by Banks (1967). Curiously, the conclusion that a high interocular pressure may confer partial protection against the development of malignant retinopathy is believed to be supported to some extent by the finding of Jain and Luthra (1967) that the

mean interocular pressure is significantly lower in diabetic persons with retinopathy than in those without retinopathy. However, an alternative and equally simple explanation would be that simple retinopathy in fact produces a fall in ocular pressure. Others have noted that the diabetic person shows little diurnal variation in intraocular pressure. Moreover, a fall in ocular pressure may be seen either in hyperglycemia produced by oral glucose loads, or contrarily by hypoglycemia produced by insulin excess. These contradictory studies seem to have been lost in a rush to believe that glaucoma may, in part, be protective of retinopathy, but further analysis of longitudinal studies of intraocular tension in diabetic patients must be made, and the relationship of these pressures to the development of vascular changes must be carefully documented.

f. NATURAL HISTORY OF DIABETIC RETINOPATHY

A description of the natural history of diabetic retinopathy is beyond the scope of this review. For additional reference, excellent reviews of the complex subject exist (Davis, Norton, and Myers, 1968; Frank, 1974). The influence of therapy on the natural history will be reviewed in the section on Treatment.

3. STATEMENT OF THE PROBLEM: DIABETIC NEPHROPATHY

Like diabetic ocular disease, only part of the renal disease in diabetic patients can be directly related to diabetic microangiopathy. An outline of the major problems of diabetic renal disease is given in Table 4, modified after Papper (1971). This table is included only to show the overall scope of this condition, and no attempt will be made to cover the pathophysiology of all the various forms of diabetic renal disease. Papillary necrosis and tubular glycogenosis (Armanni-Ebstein) are commonly seen in diabetics, but there is little reason to think of many of the other conditions listed as being exclusively related to the presence of diabetes. In reference to the glomerulus, two conditions which are well described by Hepinstall (1974) as "exudative cap lesions" and "capsular drop lesions" have been listed under sub-acute glomerulopathies. The diffuse and nodular forms of glomerulosclerosis will be considered later in some detail. The term Kimmelsteil-Wilson's "syndrome" should be referred to more specifically as Kimmelsteil-Wilson's "nodules," since the clinical correlations of proteinuria, the nephrotic syndrome, and hypertension with nodular glomerulosclerosis are poor. Before discussing specific diabetic glomerulopathies, attention will be given to infection and nephrosclerosis as manifestations of the degenerative complication of diabetes.

TABLE 4

DIABETIC RENAL DISEASE*

1.0 Interstitium (including infection)

  1.1 Acute

      1.12 Acute pyelonephritis
      1.13 Renal abscess
      1.14 Peri-renal abscess

  1.2 Chronic

      1.21 Chronic pyelonephritis
      1.22 Papillary necrosis
      1.23 Analgesic Abuse Syndrome
      1.24 Chronic Interstitial Nephritis
      1.25 Renal Tuberculosis

2.0 Tubule

  2.1 Acute tubular transport defects

  2.2 Hypokalemic nephopathy

  2.3 Tubular glycogenosis (Armanni-Ebstein)

  2.4 Obstructive nephropathy

3.0 Vascular System

  3.1 Atherosclerosis

  3.2 Nephrosclerosis

  3.3 Renal vein thrombosis

  3.4 Capillary membrane changes

4.0 Glomerulus

  4.1 Acute and sub-acute glomerulopathsis

      4.11 Exundative cap lesion
      4.12 Capular drop lesion

  4.2 Chronic glomerulopathy

      4.21 Diffuse glomerulosclerosis
      4.22 Nodular glomeruloscerosis

*Modified after Papper.

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4. STATE OF THE ART: DIABETIC NEPHROPATHY

a. PYELONEPHRITIS AND URINARY TRACT INFECTION

The risk and significance of acute urinary tract infection (acute pyelonephritis) and the resulting pathologic process in the kidney (chronic pyelonephritis) in the diabetic cannot be overemphasized. At the New England Deaconness Hospital, the frequency of pyelonephritis was 33% among diabetic males and 40% among diabetic females (Balodimos, 1971). All studies agree on the evidence that there is much more urinary tract infection among diabetic patients than among non-diabetic patients. In 1,000 consecutive patients of the Joslin Clinic, 10 or more WBC/HPF's were found in 116 patients and bacteriuria in 388 patients. By contrast, asymptomatic bacteriuria are found in 4-8% of patients in the general population.

In studies at autopsy as opposed to studies on living individuals, the frequency of changes related to urinary tract infection has been found to range from 10% to 15%. Kass (1960) noted that bacteria are present at autopsy in 40% of unselected cases with diabetes and that 15% to 20% of such patients examined at post-mortem had active pyelonephritis. Robbins and Tucker (1944) found acute pyelonephritis in 19.5% of 307 diabetic persons examined at post-mortem, and in about one third of these, it was considered the cause of death. This is a frequency of more than 4 1/2 times that found in nondiabetic patients. At the New England Deaconness Hospital, it has been estimated that acute pyelonephritis is twice as frequent as a cause of death in the diabetic as in the nondiabetic patient (Balodimos, 1971). Hepinstall (1974) has reviewed the prevalence of both acute and chronic pyelonephritis in selected series in which he felt the histologic picture as quoted by the author was consistent with the diagnosis claimed. Information adopted from this is given in Table 5.

Cystitis has been noted at autopsy in approximately 6% of diabetic patients, and an incidence of yeast infection four times greater in diabetic than in nondiabetic persons. Other infections of the urinary tract including perinephric abscess and necrotizing pyelonephritis are extremely rare and cannot be considered significant in the total epidemiology of urinary tract infection in diabetics.

Renal papillary necrosis is the term applied to ischemic necrosis of one or more renal papillae, usually in association with diabetes complicated by some other major contributory factor. The diabetic may have the papillary necrosis because of microangiopathy, pyelonephritis, or obstructive nephropathy. Edmonson and associates (1947) noted that 50% of subjects having renal papillary necrosis at autopsy were

TABLE 5

PREVALENCE OF ACUTE AND CHRONIC PYELONEPHRITIS
IN DIABETIC (D) AND NON-DIABETIC (N-D) PATTERNS*

| Author | Study | Chronic | | Acute | |
		D	N-D	D	N-D
Hepinstall, review	Autopsy	--	1.6 - 6.2	--	--
Aarseth	Autopsy	40	--	--	--
Young and Clancy	Autopsy	21	--	--	--
Gellman et al.	Biopsy	10	--	--	--
Thomsen	Biopsy	10	--	3.1	--
Aye	Autopsy	--	--	14.4	0.7
Edmondson et al.	Autopsy	--	--	12.4	3.3
Robbins and Tucker	Autopsy	--	--	6.8	1.6

*from Hepinstall (1974). See original for bibliography and discussion

diabetics and, of these, 26% had obstructive uropathy. In addition to obstruction of the urinary tract, pre-existing renal disease including nephrosclerosis and urinary tract infection itself are frequent contributing causes. Chronic ingestion of acetophenetidin is now widely accepted as one of the major causes of necrosis of the renal papillae, but there is no information on this problem in diabetic patients specifically. In terms of its overall impact, Ditscherlein (1965) found renal papillary necrosis in 46 of 400 diabetic patients or 11.5%. He noted the frequent concurrence of diabetic glomerulo-sclerosis with renal papillary necrosis in his series.

These statistics on specific pathologic entities of renal pathology are of only limited value since the renal pathology found at autopsies is likely to be a combination of glomerulosclerosis, chronic pyelonephritis, and nephrosclerosis in which no single lesion can be cited as being of primary pathologic significance.

b. NEPHROSCLEROSIS AND HYPERTENSION

Nephrosclerosis -- or, more correctly, arteriolosclerosis -- is characterized by hyaline thickening of the arterioles, especially in the efferent loop. This lesion is commonly seen in association with glomerulosclerosis but may develop in the absence of these changes. Such changes are seen to a greater degree in diabetes than in any other pathologic condition, and when seen alone without other morphologic changes should arouse suspicion of diabetes (Hepinstall, 1975). Bell (1953) reported that the arteriolar and glomerular lesions developed concurrently in the diabetic person but not necessarily together. He found arteriolosclerosis to be more common in diabetics than nondiabetics and to increase with duration of the diabetes.

In Knowles' series of patients with juvenile diabetes, 20% developed hypertension (Knowles, 1965). Sixteen of 22 patients with hypertension had renal disease which antedated the hypertension. Since these patients were not biopsied, the relation between hypertension, nephrosclerosis, and glomerular disease in this group is not known. In one autopsy series (Hepinstall, 1975), hypertension was more consistently found with the nodular (38/44) than the diffuse (45/65) lesion. Hypertension was said to be commoner in the severe forms than in the mild forms of diffuse involvement, whereas there was no such pattern in the case of the nodular type. There is excellent correlation between azotemia and the severity of the diffuse lesion, but not with the nodular lesion.

c. PATHOGENESIS OF DIABETIC NEPHROPATHY

The factors of importance in the development of diabetic nephropathy are believed to be identical with those associated with the development of retinopathy. The kidney has the advantage of being available for biopsy during life, but the eye can be studied more frequently for changes that are relatively specific by noninvasion techniques. Similarities are more striking than differences, and there is nothing to be gained by repeating the information on the relationship of the complications of the kidney to many of the correlates as has been done for the eye in an earlier section.

d. DIABETIC GLOMERULOSCLEROSIS

The development of diabetic glomerulosclerosis, also directly related to the duration of the disease, is rarely recognizable clinically in the first ten years. Nodular lesions commence with dilation of the peripheral capillary loops in the glomerulus, and abnormal mucopolysaccaride is deposited that penetrates the capillary endothelial cell. A laminated nodule results that increases in size, and appears to push capillaries ahead of it until the nodule becomes totally hyalinized. There is also involvement of the basement membrane.

Diffuse glomerulosclerosis brings a thickening of capillary walls affecting peripheral loops so that the capillary lumen is eventually occluded. As noted above, the clinical picture of proteinuria -- developing nephrotic syndrome and azotemia, frequently with hyper-tension -- is more closely correlated with the severity of the diffuse changes than with the nodular lesion.

The specificity of the nodular and diffuse forms of diabetic glomerulosclerosis in relation to the diabetic state is frequently in question. These lesions are alleged to have occurred in nondiabetic patients; however, each of these reports must be scrutinized from the point of view of a well-documented history and physical and laboratory examinations to be certain that diabetes is excluded. Since this correlation is usually made retrospectively from autopsy material, it is frequently quite impossible to rule out diabetes in patients in whom this consideration has not been made in life, and case reports finding no correlation to glucose intolerance should be reviewed with this in mind. In reference to the specificity of the nodular lesion as a mark of diabetes, Hepinstall (1974) summarized this problem by saying, "I have not seen nodular glomerulosclerosis where diabetes could definitely be excluded, but I have seen it with no glycosuria and a normal blood sugar during a terminal illness." In further description, he points out that the latency of diabetes, its ameliora-tion with advancing renal disease, and the virtual disappearance of

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mild diabetes following adrenal or pituitary scarring or necrosis are conditions in which patients with specific nodules diagnostic of diabetes might have glucose intolerance overlooked. The "capsular drop" lesion is also a distinct histologic entity appearing as a small mass in Bowman's capsule. This fact alone distinguishes it from the nodular form of glomerulonephritis. It is now considered specific for diabetes. The "fibrin cap," as the name implies, is an exudative change that has no specificity as far as diabetes is concerned. Although highly characteristic and readily identifiable, it has some superficial resemblance to the nodular lesion of diabetes but must be differentiated from it.

In living diabetics, Bryfogle and Bradley (1956) estimated the prevalence of glomerulosclerosis to be 10% in the clinic population of diabetic patients of all ages. White (1956) has stated that the frequency of glomerulosclerosis is shown by the presence of proteinuria at a range from 18% at 15 to 19 years' duration to 63% at 35 to 39 years' duration in a long-term study of juvenile diabetes. The younger diabetic population is very much at risk for glomerulosclerosis, and Knowles (1965) found the prevalence in those with known diabetes of 10 years or more to approach 100%. In the prospective observation of 167 juvenile diabetics followed beyond ten years, the cumulative risks of proteinuria at 20, 25, and 30 years' duration were 26, 37, and 48 years, respectively. As noted previously, this study by Knowles has the great advantage of being a "total" juvenile population followed throughout this period by a single physician.

Data on survival with protenuria have been developed by a number of authors, most recently by Pell and D'Alonzo (1967). These authors found that the ten-year death rates of diabetic patients with and without proteinuria were 39% and 23%, respectively, in comparison to a control rate of 10%. Among younger patients, proteinuria was noted, on the average, 14 years following the onset of diabetes, and survival after the appearance of proteinuria varied from three to 12 years. Caird's study (1968) of 134 patients with persistent proteinuria seen at the Radcliffe Clinic revealed only 28% alive after ten years, and it is noted that the life expectancy of these patients was only about half that of diabetic patients in general.

Nephropathy is responsible for about two-thirds of the deaths of patients with proliferative retinopathy who die when they are between 20 and 39 years of age. This is particularly striking in the patients having the onset of diabetes under the age of 15. This high rate is to be expected as a result of the increased prevalence of the nephropathy and retinopathy with the duration of diabetes.

In the study of 1,465 autopsied diabetic persons, Bell found glomerulosclerosis in 19.5% of the men and 30% of the women (Bell, 1953).

The fact that pyelonephritis is more common in females may well lead to some difficulty in being certain which of the major problems initiated the changes in what must be considered an "end stage kidney" at the time of death, but this is not an entirely satisfactory reason for this sex difference. In each sex, two-thirds of the cases were of the diffuse type only, and one-third included nodules as well. Kimmelsteil and Portes (1948) reported an autopsy frequency of 17% of the nodular glomerulosclerosis. Hill found in a review of 133 cases of diabetes at the Johns Hopkins Hospital a prevalence of 51% with glomerulosclerosis (quoted by Hepinstall, 1975). Of these, 37.6% had the nodular lesions and 13.5 had diffuse lesions with no accompanying nodules.

Goetez (1974) has reviewed the problem of the prevalence of azotemia in the diabetic population. He estimated the incidence of new cases of juvenile diabetes and the incidence of renal failure following duration of diabetes from ten to 30 years. On this basis, it was calculated that there were probably 0.6 new cases of azotemia due to diabetes per 100,000 population per year. This would mean that 30 new cases of azotemia would be found yearly from the juvenile diabetes population in the Minnesota area. The rapid demise of patients after beginning azotemia is alarming. The average age from onset of diabetes to onset of azotemia (creatinine 1.2 mg%) was found to be 17.3 years. Early renal failure (creatinine 2.6%), late renal failure (creatinine 8.5 mg%), and death (creatinine 12.4 mg%) followed each other in 19.4 years, 21.6 years, and 22.1 years, respectively (quoted by Goetz).

A fall in insulin requirements and some apparent improvement in glucose intolerance are sometimes seen with the onset of azotemia. There are a number of reasons why this may occur. On the one hand, the kidney plays an important role in the degrading circulating insulin; a decrease in functional renal tissue therefore has the effect of increasing the amount of insulin given. Insulin-binding antibodies may also be lost in the urine; an increasing sense of illness with azotemia leads to anorexia, and this adds to the falling glucose levels. Knowles (1974) has reviewed the overall impact of the renal disease in diabetes patients from the Joslin Clinic experience for the years 1956 through 1964 and summarized the problems as follows:

> In essence, there were 6,800 deaths in diabetic
> patients in the years 1956 through 1964 (Table 6).
> Of those listed as renal, about two-thirds were
> believed to be due to diabetic nephropathy
> (diabetic glomerulosclerosis plus arteriol-
> nephrosclerosis and sometimes pyelonephritis)
> and the remaining one-third to other renal
> disease. Although diabetic renal disease

TABLE 6

TABLE CAUSES OF DIABETIC PATIENT MORTALITY

Causes of death	Patients		Patients diagnosed at age, N	
	N	%	20 (%)	20+ (%)
Renal	615	9	229 (48)	386 (6)
Cardio-vascular	4,613	67	132 (28)	4,481 (71)
Other	1,572	23	111 (24)	1,461 (23)
Total	6,800	99	472 (100)	6,328 (100)

The problems related to therapy of azotemia in diabetic patients include the use of special diet, dialysis and renal transplantation. These will be described in the section on Treatment.

accounted for only 6 percent of deaths in the
total population, it was the cause in almost
one-half of those in the younger patients. In
older diabetic patients, the morbidity of renal
disease is markedly outranked by that of large
vessel disease.

It is difficult to estimate a yearly death
rate from diabetic renal disease. About 40,000
persons are listed as dying yearly with diabetes
mellitus given as the leading cause of death.
According to the above, 3,200 of these would
die from diabetic renal disease. This estimate
may be conservative, however, for listings on
death certificates are not always complete.
Another approach is to estimate the number of
young diabetic patients living at a given time.
With a population of approximately 200 million
and known prevalence of diabetes mellitus of
1.61% (with 8% being diagnosed at age 25 or
less), there would be 129,000 juvenile diabetic
patients now living. One-half, or 65,000, will
die of renal disease at a rate of 2,500 per year
if a median duration of life of 25 years after
diabetic diagnosis is assumed. This figure plus
additions for older diabetics dying would
approach that of 3,200 given above. This would
indicate a yearly loss of 30 patients in an area
of 2 million population. Again, this figure
seems low when surveys of hospital deaths are
made (Knowles).

B.   REPORT OF WORKGROUP ON MACROVASCULAR DISEASE*

1.   STATEMENT OF THE PROBLEM AND ITS IMPACT

Disease of the large blood vessels resulting from diabetes is one
of the major health problems in the United States. A precise ranking
of its importance will depend on the development of more information
through research. It is, however, evident that atherosclerosis
secondary to diabetes is among the top four killers of Americans.
This contention is based on considerations which include the following:

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* Prepared by Dr. Kelly West et al.

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a. Coronary heart disease is by far the leading killer of Americans. Coronary disease accounts for about 700,000 deaths yearly. This represents about one-third of all deaths. Diabetes and occult diabetes account for a substantial share of these deaths (see below).

b. Risk of death from coronary disease varies considerably among the subelements of the total population of U.S. diabetics. For example, rates of coronary disease are high in elderly nondiabetics, exceeded only slightly by those in elderly diabetics. On the other hand, diabetic persons in their fourth and fifth decades of life have more than ten times as much coronary disease as nondiabetics. Considering the entire universe of diabetics, rates of coronary disease and coronary death are about twice as high in diabetics as in nondiabetics.

Death certificates of patients who die of coronary disease mention diabetes in about 10% of cases. Moreover, there is evidence that in a substantial percentage of diabetic patients who die from coronary disease, diabetes is not mentioned on the death certificate. This very large group includes three subgroups. The first consists of persons with known diabetes in whom the condition is not mentioned on the death certificate. The second consists of persons with occult diabetes. The size of this group depends upon the definition of the term "diabetes," but this group is probably at least as large as the group with known diabetes. In this latter group, the increased risk of coronary disease is probably less than in those with known diabetes, but it is appreciable. A third subgroup consists of those with borderline or slightly impaired glucose tolerance in whom there is uncertainty and disagreement concerning whether they should bear the designation "diabetic." Nevertheless, there is impressive evidence that these individuals also have increased risk of coronary disease.

Even if one assumes that only half of coronary disease in known diabetic patients is attributable to diabetes, and even if one assumes that only 25% of coronary disease in occult diabetes is attributable to diabetes, diabetes emerges as a major factor in the etiology of coronary disease in the United States. Recent studies in Tecumseh, Michigan, suggest that a portion of the middle-aged population as great as 20% may have increased risk of coronary disease as a result of impairment of glucose tolerance. These studies are consistent with the possibility that hyperglycemia is the leading cause of coronary disease.

Most studies have shown that gross elevations of serum cholesterol are even more disadvantageous than elevations of blood glucose.

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However, by certain definitions, elevations of the blood glucose are more common in the population at risk than "abnormal" serum cholesterol values. If one assumes that most Americans have abnormal serum cholesterol values, then this factor would properly be considered the main cause of coronary disease. On the other hand, if only 5% are considered to have abnormal cholesterol values, then "hypercholesterolemia" would probably not be as important as "hyperglycemia" (as defined by traditional standards) as a factor in coronary disease. An any rate, hyperglycemia is, together with hyperlipidemia and hypertension, a major factor in accounting for the frequency of coronary disease.

Studies by the National Center for Health Statistics of death certificate data reveal that in individuals from 45 to 64 years of age in whom diabetes was described as the underlying cause of death, arteriosclerotic heart disease was mentioned 12 times as frequently as in certificates in which death was due to some other underlying cause (Publication No. 10 from Series 20, 1971). Evidence of the kind cited above would suggest that diabetes and hyperglycemia account for roughly 20% of coronary disease. Since there are about 700,000 deaths yearly from coronary disease, diabetes could be assigned responsibility for about 140,000 of these, a number more than twice as great as the number of deaths from any single type of cancer. It is also more than twice the number of deaths from auto accidents.

About 25% of those with known diabetes, or approximately one million people, are under care for heart disease.

c. To this massive toll from diabetic coronary disease, one must add the cost of the enhancement by diabetes of atherosclerosis in other large vessel systems. This relates mainly to disease of the arteries of the legs and brain. Rates and types of strokes vary considerably among the population of diabetic patients, depending upon age, duration of diabetes, and other factors. On the whole, it appears that stroke is about twice as common in diabetics as in nondiabetics. Gangrene, requiring amputation, is probably about 20 times more common in diabetics than in nondiabetics. Diabetes accounts for approximately half of all leg amputations. About 75% of deaths in diabetic patients are attributable to large vessel disease. Even in juvenile diabetics, macrovascular disease is a major cause of morbidity and mortality. In juvenile diabetics who have had diabetes less than 25 years, micro-angiopathy is a more important cause of death than macroangiopathy. However, in juvenile diabetics who survive more than 25 years (the majority), large vessel disease is a more significant cause of death than small vessel disease.

Recent studies suggest that the total number of deaths with known diabetes is roughly 600,000 per year. This was based on studies of the prevalence of diabetes in individuals in whom diabetes was not mentioned

on the death certificate. If approximately 75% of these deaths are
assigned to all types of macrovascular disease, the number of deaths
from diabetic macrovascular disease is approximately 450,000 per year.
To this latter toll must be added a very considerable number relating
to the effect of occult diabetes on death from large vessel disease.
When this is done, the toll from diabetic macrovascular disease
approaches one million annually. As pointed out above, it is not
appropriate to assign all the responsibility for death to diabetes in
the universe of persons who have both hyperglycemia and vascular
disease. Even assuming, however, that only 40% of the responsibility
for death in these persons should be ascribed to diabetes, the number
is roughly equivalent to the number of deaths from all kinds of
cancer combined. In Americans under 70 years of age, there are four
leading killers of approximately equal importance: diabetes, hyper-
lipoproteinemia, hypertension, and cancer.

d. Knowledge concerning the scope and impact of diabetic macro-
vascular disease is quite incomplete. These problems have received
far less attention than their importance would indicate. There are
several reasons for this, including the fact that diabetes is a
"silent killer." Diabetics of mild to moderate severity (the majority)
often feel well while developing macrovascular disease that will
produce serious and disabling complications or death.

2. STATE OF THE ART

a. INTRODUCTION

Several recent reviews have summarized very well the state of
present knowledge and gaps to be filled in this field. A huge amount
of information is contained in the newer editions of the standard
textbooks on diabetes, edited by Marble and associates, and by
Ellenberg and Rifkin. With respect to scope and impact of the large
vessel lesions, there is much information in the Joslin text, especially
in the chapters by Krall, Marks, Entmacher, and Bradley. Tzagournis
has recently reviewed this subject (1975). The Diabetes Source Book
of HEW (1969) also contains important information. An alphabetized
list of more than 500 references attached to this report will give
details concerning citations mentioned below. These include data
gathered by insurance companies that provide important and unique
information. Recently the Fogarty International Center of the National
Institutes of Health sponsored a conference on diabetes, the proceedings
of which are presently being published through the U.S. Government
Printing Office. A draft pre-publication copy was made available

to the Commission. Several of the chapters in this document summarize very well some of the important information on the scope and impact of macrovascular disease in diabetes. These essays included those by Knowles, Prout, and Meinert, and by Ostrander and Epstein.

Since this report concerns only the scope, impact, and epidemiology of macrovascular disease in diabetes, important observations and potentialities relating to basic and clinical investigations are mentioned only when they have implications relating to these concerns. The importance of basic and clinical research, including the patho-physiology of diabetic macrovascular disease, will be stressed in other sections of the Commission Report.

Diabetes seems to enhance the rate of development of atherosclerosis in all elements of the vascular tree. Through epidemiologic approaches and by other means, it has been shown that both intimal atherosclerosis and medial sclerosis are increased substantially in diabetes. Even when diabetics are matched for age and sex with nondiabetics, they differ in several respects. This makes it difficult to determine the extent to which the increased rates of vascular disease in diabetics are directly attributable to diabetes and the extent to which they are related to factors often associated with diabetes, such as obesity and elevated levels of serum triglycerides. This is one of the main challenges for epidemiologic investigators.

Nilsson (1967) found that arcus senilis was present four times more frequently in diabetics than in nondiabetics. In all societies, higher rates of atherosclerosis have been found in diabetic persons than in nondiabetics. But in many societies, the rates of athero-sclerosis in diabetic patients are far lower than in Americans. The limited amounts of evidence available at present on this subject suggest that the relative immunity to atherosclerosis in some groups with diabetes is not primarily the result of racial factors. This suggests strongly the exciting possibility that the large vessel lesions of diabetes are preventable. It is clearly not feasible, and not even desirable, that American diabetic patients adopt the same way of life as those of Nigeria, rural Japan, or Guatemala. On the other hand, detailed studies of the factors with which immunity and enhancement are associated will surely identify certain factors that will make possible the development of preventive measures.

Although there seems to be a general enhancement of atherosclerosis and of medial sclerosis and calcification throughout the body, the effect of diabetes on large vessels does vary appreciably in different parts of the arterial tree. For this reason a separate discussion will be provided below for each of the three main systems affected (coronary disease, cerebral disease, and leg disease).

b. CORONARY DISEASE

1) Effect of Diabetes on Death Rates

The discussion above has summarized present evidence with respect to the massive importance of diabetes to coronary disease. In particular, the importance of diabetic coronary disease as a cause of death was stressed. Data of Kessler (1971) suggest that a very substantial majority of the excessive deaths from diabetes (as compared to the general population) are attributable to the increase in rates of coronary disease in diabetics. Westlund (1969) performed one of the better studies relating causes of death in a general population to the presence or apparent absence of diabetes. He also concluded that the most prominent source of excessive deaths from diabetes was the excess of deaths from coronary disease. In this study of the citizens of Oslo, Norway, death from coronary disease in diabetic males was 4.3 times more common than in non-diabetic males, and in diabetic females the rate was 8.6 times greater than in nondiabetic females. The rate of death from coronary disease was, however, somewhat higher in diabetic males than in diabetic females.

Data reported by the insurance companies also suggest strongly that the major cause of excessive death rates in diabetes is diabetic coronary disease. Typical of such reports was that of Entmacher (1972). Similar results were reported by Goodkin (1969). A study in Malmo, Sweden, by Sievers (1961) and his associates showed that the frequency of myocardial infarction in diabetic persons was five times greater than in persons with no apparent diabetes. In some populations, the excessive rates of death from coronary disease in diabetics have been of more modest degree. Reporting on deaths in Birmingham, England, Hayward and Lucena found that diabetic women had an excess rate of 1.8, while men had an excess rate of 1.6. In their studies in Sweden, Gronberg and his associates (1967) found little effect of diabetes on rates of large vessel disease after corrections were made for factors such as age. It is not clear whether the lesser effect of diabetes in this particular population was apparent or real.

2) Report of the Inter-Society Commission

In 1970, a special panel of experts on atherosclerosis that included groups chaired by Stamler and by Lilienfeld published in Circulation a document on primary prevention of the atherosclerotic diseases. They indicated that "clinical diabetes mellitus has been recognized for years as a serious risk factor for atherosclerotic disease." They cited investigations showing that "diabetics have

atherosclerotic disease more often, more severely, and more prematurely than nondiabetics." Their report concluded: "...long term prospective studies in U.S. population groups indicated that asymptomatic hyper-glycemia -- so-called chemical or subclinical diabetes -- is also an independent risk factor for atherosclerotic disease of major coronary, cerebral, and peripheral arteries."

In studies conducted under a variety of circumstances, some of which are cited here, diabetes is usually found to be a strong risk factor in coronary disease. However, in a few circumstances this has not been observed. On the basis of his studies in Ireland, Mulcahy and his associates (1969) thought the importance of diabetes as a risk factor was significant but not major. Results and conclusions of this kind do not necessarily contradict the substantial majority. In many populations of diabetics outside the United States, risk of coronary disease is modest despite the presence of marked hyperglycemia. This will receive further discussion later. At this point, it should be stressed that apparent differences in the potency of diabetes as a risk factor deserve further study, since they may provide clues concerning the development of preventive measures.

3) Effect of Diabetes on Morbidity

The high rates of death from diabetic coronary disease are paralleled by a high incidence and prevalence of manifestations and morbidity from coronary disease in diabetics. Bauer reported in a publication of the National Center for Health Statistics (1967) that 21% of American diabetic patients said they had "a heart condition." It seems very likely that rates of heart disease are far higher than this because of the appreciable rates of occult heart disease and the relative insensitivity of this method of ascertaining the prevalence of heart disease. When examinations were performed in a series of diabetic patients, Liebow (1955) found 40% had evidence of coronary disease. Bradley and Bryfogle (1956) found 42%.

Medalie (1973) studied the incidence of angina pectoris in a population of 10,000 men in Israel. Random glucose determinations were performed on blood at the outset of the study. In those in whom random blood glucose levels were below 130, the incidence of angina pectoris over a period of five years was 3.6%. In those with borderline glucose values (130-159), the incidence of angina was 7.3%, while in those with clearly elevated blood glucose levels (greater than 159 mgs %), the rate of angina was 9.3%. In this population, relative weight had little effect on risk of angina. Thus, the excessive rate in hyperglycemic individuals was not attributable to their greater weight. In their studies of a whole population in Bedford, England, Keen and

his associates (1965) found evidence of coronary disease much more frequently in diabetic persons than in those with normal glucose tolerance. Rates of manifestations of coronary disease were intermediate in those with borderline glucose tolerance. These differences were not attributable to age or blood pressure differences between the diabetics and nondiabetics.

Garcia and his associates (1974) have recently summarized their experiences in Framingham. Although the number of known diabetics in this population is rather small (239), other aspects of these circumstances are relatively ideal for investigating the effects of diabetes on vascular disease. The rate of cardiovascular morbidity was 84% higher in diabetic patients than in those with no apparent diabetes. Death from cardiovascular disease was about three times more frequent in the diabetic persons. In patients taking insulin, the rate of death was 4.3 times greater than in those with no apparent diabetes. Only a small portion of the excessive risk in the diabetic persons appeared to be due to associated factors such as their greater adiposity and their higher triglyceride levels.

In Sudbury, Massachusetts, O'Sullivan and his associates (1970) found electrocardiographic abnormalities were about three times more common in diabetics than in age-matched controls. Rates of electrocardiographic abnormalities were intermediate in subjects with mild hyperglycemia. Data from the studies of a general population in Tecumseh, Michigan, have been summarized in several reports by Ostrander (1973), Epstein (1967), and Hayner (1965). These studies show a profound effect of hyperglycemia on risk of morbidity and mortality from coronary disease. These effects of hyperglycemia were largely independent of other factors such as blood pressure and serum lipid levels.

In the recent edition of Joslin's textbook on diabetes, Bradley (1971) summarizes a great deal of evidence gathered by him and others indicating the high risk of both morbidity and mortality from coronary disease in diabetics. In their studies of the general population of six Central American republics, West and Kalbfleisch (1971) found electrocardiographic abnormalities much more frequently in subjects with hyperglycemia than in age-matched subjects with normal glucose tolerance. Pell and D'Alonzo (1963) showed that risk of coronary disease was much higher in diabetic patients than in nondiabetics of the same population. Stamler (1973) has recently reviewed evidence from several sources, including his own studies, linking hyperglycemia and coronary disease.

4) <u>Coronary Disease and Glucose Tolerance</u>

Many investigators have measured the prevalence of impaired glucose tolerance in patients with coronary disease and other types of large vessel disease. Most of the studies are difficult to evaluate because of the lack of control subjects or because control groups do not satisfactorily match the characteristics of the group with vascular lesions. Also, some of these tests on subjects with vascular lesions were performed at times in which conditions were not basal (e.g., during periods of inactivity, acute or subacute illness, etc.). With few exceptions, rates of impairment of glucose tolerance in patients with coronary disease have been impressively high, rates up to 76% having been reported. In general, if considered in the aggregate, this evidence suggests that about one-third to one-half of Americans with known coronary disease have impairment of glucose tolerance. One of the better studies of this kind was that of Wahlberg (1966), who also reviewed the literature on this subject. He combined the data from 12 different studies on rates of impairment of oral glucose tolerance in patients with cardiovascular disease and found that 61% had exhibited "abnormal glucose tolerance."

As pointed out previously, control groups in these series were sometimes unsatisfactory. In the subjects studied by Wahlberg -- subjects who had coronary disease -- the prevalence by his criteria of abnormal intravenous glucose tolerance was 31% in subjects with coronary disease, while only 4% of the control group had impairment of tolerance by these standards. The rate of impaired glucose tolerance was 34% in those with angina pectoris and 30% in those who had previously sustained myocardial infarction. In some of the studies of this kind, it seems likely that the high rates of impaired tolerance are in part attributable to the greater adiposity of patients with coronary disease, but it seems unlikely that this is the dominant factor.

Rates of impairment of glucose tolerance are particularly high in young adults who sustain myocardial infarction. In studies of Heinle et al. (1969) in patients with coronary disease, about two-thirds of the patients had impaired intravenous glucose tolerance, with the rate approximately the same for patients in the fifth, sixth, and seventh decades of life. On the other hand, the disparity in rates of impaired tolerance between those with and without coronary disease was much greater in the subjects in the fifth decade of life. High rates of impaired tolerance in young patients with coronary disease have also been reported by Tzagournis et al. (1968) and by Falsetti (1970).

5) Effect of Diabetes on Prognosis

        Most studies have shown that prognosis is worse in diabetic
patients than in nondiabetics when coronary disease is present. Some
of this evidence has been cited above. Studies from large and less
selected populations of patients with myocardial infarction and of
coronary disease are of particular interest with respect to a determina-
tion of the effects of the presence of diabetes.

        Krolewski et al. (1975) recently reported their experience with
172 diabetics treated for myocardial infarction in five hospital
"departments for internal disease" in Warsaw, Poland. Rates of death
during hospitalization were approximately twice as high in diabetic
persons as in controls. Higher rates of death with myocardial infarc-
tion in diabetes have been reported previously by Bradley et al. (1956),
by Sievers (1963), and by Partamian et al. (1965). Soler and his
associates (1974) found mortality rates only slightly higher with
myocardial infarction in diabetic patients treated with diet alone
when these were compared to rates of mortality in nondiabetics with
myocardial infarction.

        In diabetics being treated with insulin or oral hypoglycemic
agents, rates of death were substantially higher with myocardial
infarction than in the control group of nondiabetics. Weinblatt et al.
(1973) studied myocardial infarction in a population of 110,000
insured persons. In a group of 129 females with myocardial infarction
were 29 women with diabetes. In these 29 women, the rate of death in
the first month was very high (62%), as compared to a fatality rate
of 29% in the control group of women. In diabetic men with infarction,
the rate of death in the first month was 35%, a figure not significantly
different from the slightly lower rate in the controls (32%).

        Mortality rates were also studied by Weinblatt et al. over a
period of 4.5 years in patients with angina pectoris. In diabetic
men, death rates were 32% as compared to 15% in the nondiabetics with
angina. Only 8% of nondiabetic women with angina died, while 35% of
the diabetic women with angina died. It did not appear that this bad
prognosis was explained by differences among the latter groups in
levels of serum cholesterol or of blood pressure. Particularly high
rates of mortality have not been observed in all studies in which
diabetic patients were compared to nondiabetics. For example, in
studying 400 consecutive cases admitted to a coronary care unit in
Stockholm, Helmers (1973) found no evidence of excessive mortality
in the subgroup of 40 clinical diabetics. Under the circumstances
of their observations, Reynertson and Tzagournis (1973) found no
relationship between status of glucose tolerance and survival in
137 patients with coronary heart disease studied prospectively.

In a prospective study of a large number of patients in whom coronary arteriography had been performed, Bruschke (1973) at the Cleveland Clinic found that the presence of diabetes had a profound effect on prognosis. In this study, the level of serum cholesterol had no effect on five-year cardiac mortality, but rates of death were twice as high in those with diabetes as for those with no apparent diabetes. In these circumstances, obesity and hypertension had no effect on prognosis and cigarette smoking only slight effect. In patients with impairment of glucose tolerance but without clinical diabetes, prognosis was intermediate between that of known diabetics and those with normal glucose tolerance.

6) Special Features

There are several special features of diabetic coronary disease. The presence of diabetes seems to remove all or almost all of the immunity of middle-aged women to coronary disease. In most series, rates of coronary disease are approximately as high in diabetic women as in diabetic men. This is in sharp contrast to the ratio of these rates in nondiabetic men and women who are in their fourth, fifth, or sixth decades of life. For example, in affluent societies, rates of coronary disease for men in their fifth decade of life are usually several times higher than in women. Data of the investigators of the Joslin Clinic show this phenomenon very well. This experience is outlined in some detail in various sections of the most recent edition of Joslin's book, now edited by Marble (1971).

Kessler (1971) found that in diabetic men the death rate from coronary disease was 50% higher than in age-matched controls, while rates of coronary death in diabetic women were 110% higher than in age-matched women with no apparent diabetes. Kannel et al. (1974) found in Framingham that in diabetic men congestive heart failure was about twice as common as in men with no apparent diabetes. On the other hand, congestive failure was five times more common in diabetic women than in women with no apparent diabetes.

In Framingham, the prevalence of cardiovascular morbidity was 64% higher in the diabetic men than in the general population of men, but in diabetic women rates were even more elevated (125% greater than the general population of women). Engel et al. (1974) studied 21 women with demonstrated coronary disease under 41 years of age, finding 11 (52%) with impairment of glucose tolerance. Bengtsson et al. (1973) studied ischemic heart disease in women of Goteborg, Sweden. The rate of clinical diabetes in women with myocardial infarction was 15%, while in age-matched women from the general population, the rate of clinical diabetes was 1%. However, in this

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population, the rates of angina pectoris and of electrocardiographic changes were not higher in the women with clinical diabetes. Moreover, in the women in whom diabetes had not been previously diagnosed, there was no relationship between the presence of angina or myocardial infarction and the status of glucose tolerance.

In a New Zealand population, Bailey and Beaven (1968) studied a series of patients with myocardial infarction drawn from a population in which rates of known diabetes were estimated at about 4% in this age group. The rate of "established" diabetes in men with infarction was 6%. In women with infarction, 12% had established diabetes. Liebow et al. (1964) found that one-third of a group of 58 women had definite cardiac abnormalities at the time of first diagnosis of diabetes. Weaver and associates (1970) found that 34 of 90 women with newly diagnosed diabetes had cardiac abnormalities.

7) Factors Other Than Atherosclerosis

Other features of coronary disease in diabetics suggest a need to determine the extent to which increase of susceptibility is attributable to factors other than the increased amounts of atherosclerosis. In general, levels of blood pressure and adiposity are higher in diabetics. As indicated earlier, these factors do not appear to account for a major share of the excessive rates of coronary disease in diabetes. In the studies of Bruschke et al. (1973) on patients who had coronary arteriography, the poorer prognosis of the diabetics does not appear to be explained entirely on the basis of their greater degree of occlusive disease.

Hamby et al. (1974) reported high rates of diabetes in patients with idiopathic cardiomyopathy. Autopsies performed on four of these diabetic patients revealed that the larger coronary arteries were free of arteriosclerosis. The researchers speculated that the morbidity might have been due to changes observed in small coronary vessels. Similar conclusions had been reached in 1960 by Blumentahl and Goldenberg, who reported the presence of lesions in small intramural coronary vessels in diabetic patients. It is not clear, however, whether these lesions have functional significance, and their extent and character are the subject of some disagreement. Ledet (1967), who performed extensive studies of the coronary vasculature to compare diabetic and nondiabetic persons, found that severe PAS-positive deposits were much more common in the smallest intramural branches in diabetics. However, there was no measurable difference in the wall thickness of these vessels between diabetic and nondiabetic patients. Endothelial proliferation was not observed in the small vessels with PAS-positive material.

Ahmed and associates (1975) have reported abnormal cardiac muscle function in both experimental diabetes and in diabetics without evident occlusive disease of the large vessels. Ettinger et al. (1971) reported high rates of impaired glucose tolerance in patients with idiopathic cardiomyopathy. Kannel et al. (1974), calling attention to the very high rates of congestive failure in diabetic patients, concluded that these high rates were probably not entirely attributable to atherosclerosis of the main coronary channel. Some of this excessive rate of congestive failure, they thought, was probably the result of either small vessel disease or metabolic aberrations.

Margolis et al. (1973) reported that rates of unrecognized myocardial infarction were considerably higher in diabetic patients than in nondiabetics from the Framingham population. Of electro-cardiographically documented myocardial infarctions, 22% had not been clinically evident in the nondiabetics. In the diabetics, 39% were occult.

Possibly small vessel disease could impair myocardial function directly, and it is conceivable that it could in some way accelerate the atherosclerotic changes in the walls of the large vessels of the coronary tree. Another possibility is that neurologic changes might produce deleterious effects on myocardial function. Although epidemiologic studies have considerable potential for elucidating the inter-relationships among large vessel disease, small vessel disease, and neurologic pathology, previous epidemiologic designs have not yielded much information in this respect.

8) Importance of Blood Glucose Levels

One of the most important questions remaining is the degree to which extent and duration of hyperglycemia are responsible for the rate at which coronary atherosclerosis develops. The same question applies with respect to the other large vessel and small vessel lesions of diabetes. A closely related question is whether the mitigation of elevated blood glucose levels can slow the rate of development of large vessel disease.

Present evidence in this respect is even less decisive than that concerning the association of hyperglycemia and small vessel disease. Many of the previous clinical and epidemiologic studies identified no relationship between levels of hyperglycemia and rates or amounts of large vessel disease. Indeed, in some, no relationship was found between duration of hyperglycemia and large vessel disease. Typical of these studies were those of Weaver et al. (1970), who found rates of cardiovascular disease to be about the same in women with newly

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diagnosed diabetes and women with diabetes of substantially longer duration. Findings of Martin and Warned (1975) were similar in a small group of diabetics. Oakley et al. (1974) reported the results in a group of diabetics who had survived more than four years. They were unable to identify any striking clues that would account for the fortunate outcome in this group. It may be significant, however, that these people were as a group rather lean, and blood pressure levels were low. These authors were not certain that blood glucose levels had been any better controlled in this group than in the group who died at an earlier stage of diabetes.

Gottlieb (1974) studied long-duration diabetic patients who had low rates of vascular disease (small and large vessels). They were lean, with low blood pressures. He concluded that their control of hyperglycemia had been better than that generally prevailing. Under the circumstances of their study, the University Group Diabetes Program found no evidence that lowering blood glucose levels to a modest degree over a period of several years had any protective effect on large vessels.

In interpreting studies that seem to show either a positive or negative effect of control of blood glucose, several factors must be kept in mind. One is that a more favorable outcome in those with lower blood glucose might conceivably be attributable to mildness of several aspects of the disease process. Thus, the association of lower glucose values and favorable outcome is not necessarily a relationship of cause and effect. On the other hand, it must be kept in mind that older individuals on the whole have lower blood glucose levels and less severe diabetes. Since older people have more large vessel disease from factors other than hyperglycemia, the failure to show relationship between degree of hyperglycemia and large vessel disease could in some circumstances be attributable to the older age of those with mild hyperglycemia.

Duration of diabetes is difficult to determine, particularly in older persons. Disparity between duration of known diabetes and actual duration of diabetes tends to be greater in patients with mild diabetes. This makes difficult the interpretation of evidence purporting to show the presence or absence of a relationship between hyperglycemia and vascular disease. Another consideration is that there is a strong relationship between age and duration of diabetes. The analyses of many studies have failed to take into account the need to correct data on duration of diabetes for age. In fact, most series of diabetic patients are too small to make these and several other corrections required in assessing the relationship of degree of hyperglycemia and vascular disease. Even with ideal study designs, including factors such as the obtaining of representative samples of diabetic persons,

total sample sizes of more than 500 are required to provide numbers adequate to permit the appropriate matching and correction for the many factors that influence rates of large vessel disease. These factors probably include degree of hyperglycemia, duration of hyperglycemia, age, serum lipid levels, blood pressure, smoking, and others. Among many other factors that may need to be included in the matching process are adiposity, blood insulin levels, diet before and after discovery of diabetes, and type of medication. For these reasons certain important questions will require study groups that include several hundred or even thousands of diabetics.

Although far from ideal in some respects, data of the insurance companies offer several special potentialities. One is large numbers. Another important asset is that experience in various elements of the diabetic population can be appropriately matched with those in the same population who do not have diabetes. Some examples may be given that will illustrate these points rather well. Risk of death from large vessel disease in insured diabetic persons is much greater in those in the sixth and seventh decades of life than in the fourth and fifth decades, even though the older subjects have in general lower blood glucose levels and milder diabetes. However, this by no means justifies the conclusion often drawn that these circumstances show the lack of effect of degree of hyperglycemia on risk of large vessel disease. This is brought out best by data in which appropriate matching is applied both for age and duration of diabetes.

One method for implementing this matching, all too seldom applied, is commonly employed by insurance companies when they relate risk of death in persons with a certain condition to risk of death in persons of the same age who do not have the condition. The attached tables prepared by Goodkin (Tables 7 and 8) are illustrative. In the upper table, the bottom figure at the far right shows that risk of death in the entire universe of insurance applicants was 430%, 4.3 times the standard rate. On the other hand, the increased risk of death in the persons over 60 is much more modest (247). In contrast, risk of death when expressed in this fashion is higher in younger persons with greater degrees of hyperglycemia. For example, in persons in the third decade of life, rates are more than five times higher in diabetic patients than in the standard population of the same age. The bottom table shows that outcome is far better in patients who were judged at the time of application to have satisfactory control of diabetes.

While these data alone can not be regarded as decisive because of many other problems in interpretation, they do match for two important factors (age and type of treatment) and also provide larger numbers than are usually available. In individuals taking insulin

TABLE 7

MORTALITY BY AGE AT DIAGNOSIS OF DIABETES

	ISSUED				DECLINED				ALL			
Age	Entrants	Actual Deaths	Expected Deaths	A/E Ratio	Entrants	Actual Deaths	Expected Deaths	A/E Ratio	Entrants	Actual Deaths	Expected Deaths	A/E Ratio
Under 15	111	8	1.40	571%	598	97	5.38	1,803%	709	105	8.78	1,549%
15-19	121	8	1.37	584	359	60	3.92	1,531	480	68	5.29	1,285
20-29	324	7	5.10	137	678	80	11.68	685	1,002	87	18.78	518
30-39	357	12	8.50	141	721	104	20.94	497	1,078	118	29.44	394
40-49	300	28	14.72	190	723	180	37.75	477	1,023	208	52.47	398
50-59	124	14	9.89	142	452	96	35.92	267	578	110	45.81	240
60 & over	5	–	.45		101	28	10.89	257	103	28	11.34	247
ALL AGES	1,342	77	41.43	186%	3,632	645	126.48	510%	4,974	722	167.91	430%

*A/E ratios not shown for less than five deaths.

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TABLE 8

MORTALITY BY CONTROL OF DIABETES

Type of Control (Units)	Controlled (a)				Poor Control (b)			
	Entrants	Actual Deaths	Expected Deaths	A/E Ratio (%)	Entrants	Actual Deaths	Expected Deaths	A/E Ratio (%)
Insulin, less than 50 units	560	35	17.84	196	292	34	7.87	432
50-74	192	13	3.64	357	155	20	2.41	830
75 or more	44	1	1.12	.	55	6	1.14	526
Amount unknown	8	1	.35	.	14	-	.17	-
All with insulin...................	804	50	22.96	218	516	60	11.59	518
No insulin, oral medication, or diet only....	460	24	15.83	152	140	22	5.93	371
ALL CASES........................	1,264	74	38.78	191	658	82	17.52	468

(a) Issued cases
(b) Cases declined for the following reasons:

   1. Excessive glycosuria or poor blood sugar tests on examination only.
   2. History of recent high blood sugar.
   3. History of coma or insulin shock only.

A/E ratios not shown for less than five deaths

judged to have satisfactory control, the rates of death were about twice that of a standard age type and matched group, while in those on insulin judged to have poor control, the risk of death was increased by a factor of five.

In patients who did not take insulin judged to have satisfactory control, risk of death was 152% of the standard risk; but in those judged to have poor control who did not take insulin, risk of death was 371% of standard. It is also important here that judgments of adequacy of control were made at the time of application rather than after death. Other data show that except in the patients who died before age 30, a substantial majority of the deaths in all other subgroups of diabetic persons are attributable to large vessel disease. This and other considerations suggest that any large differences in mortality among subgroups are very likely to be related to differences in rates of death from large vessel disease.

Although data on the relationship of duration of hyperglycemia and risk of coronary disease are conflicting, some suggest very strongly a positive effect of duration. Bradley (1971) reported that in a subgroup of 45 long-duration diabetic patients, coronary disease caused deaths in 100%!

In 1971, the National Library of Medicine published a bibliography of 130 citations on the effect of metabolic control on maturity-onset diabetes. This publication is cited in the references under the letter B (bibliography). Another study in which outcome was analyzed after appropriate correction for age was that reported by Garcia and his colleagues from Framingham (1974). These results coincided with those reported above based on the experience of the insurance companies. Risk of death from coronary heart disease was only 1.1 times that of standard in a small group of diabetics being treated on diet alone. In those on oral agents, risk of death from coronary disease was 2.4 times the expected rate, while those on insulin had a death rate from coronary disease that was 4.3 times standard. While these circumstances do not prove that rate of large vessel disease is influenced directly by the degree of hyperglycemia, they are quite compatible with that hypothesis. Data of Pell and D'Alonzo (1970) of Ryan (1970), and of Redisch et al. (1974) also support this hypothesis.

Another table of Goodkin (Table 9) shows the strong relationship of duration of diabetes to death rate after correction for age. This gives considerable support to the notion that hyperglycemia itself is harmful.

TABLE 9

BY AGE AND DURATION OF DIABETES AT TIME OF APPLICATION--ISSUED AND DECLINED

Duration of Diabetes at Time of Application (in Year)	Entrants	Actual Death	A/E Ratio (%)	Entrants	Actual Death	A/E Ratio (%)
		Ages 10-19			Ages 40-49	
0- 5	110	7	-	687	85	336
6-10	48	-	-	291	40	375
11-14	29	1	-	122	42	282
15-19	8	-	-	110	19	488
20 & over			-	112	22	587
	195	8	678	1,322	178	372
		Ages 20-29			Ages 50-59	
0- 5	345	19	686	567	95	240
6-10	246	22	1,146	182	57	427
11-14	177	31	2,153	79	29	642
15-19	109	19	2,159	62	21	504
20 & over	71	18	2,712	51	17	572
	948	107	1,408	941	219	339
		Ages 30-39			Ages 60 & over	
0- 5	557	32	411	145	35	227
6-10	258	18	465	66	22	302
11-14	160	22	944	16	6	283
15-19	155	28	1,315	21	9	396
20 & over	163	30	1,408	17	-8	620
All	1,303	130	712	265	80	283

A/E ratios not shown for less than five deaths.

9) Factors Other Than Hyperglycemia

Even if the rate of large vessel disease is closely associated with degree of hyperglycemia, mitigation of diabetic large vessel disease would not necessarily be wholly dependent upon melioration of hyperglycemia. For example, it might be that the deleterious effects of a given degree of hyperglycemia could be reduced by correcting certain changes produced by that aberration. These might include, for example, correction of changes in viscosity, coagulability, platelet aggregation, enzymatic or osmotic effects, and disturbed lipid metabolism. Epidemiologic studies in special populations strongly suggest this possibility.

West (1974) recently reviewed a series of studies and clinical observations in aboriginal New World populations. Profound differences were found in rates of large vessel disease in groups of diabetic persons that could not be accounted for by differences in levels of hyperglycemia. For example, both Saiki and Rimoin (1968) and Prosnitz and Mandell (1967) have reported very low rates of large vessel disease in Navajo patients despite high levels of glycemia. Tulloch has summarized results of various studies in South African diabetic populations with respect to the prevalence of vascular disease. Very substantial differences have been observed which appear unlikely to be due to differences in levels of glycemia. Wicks and Jones (1974) reviewed 100,000 consecutive missions to Harare Hospital, which serves the African population of Rhodesia. Diabetes was seen rather commonly. For example, in a single year, 107 cases were diagnosed. Despite this, not a single case of myocardial infarction was observed in a diabetic patient.

In a very large hospital serving black inpatients and outpatients of Johannesburg, Seftel (1964) had never seen a diabetic patient with myocardial infarction prior to 1958. Since that time coronary disease has been encountered occasionally in these diabetic persons, but the frequency is dramatically less than in U.S. blacks, despite high levels of blood glucose. Both Greenwood (1968) and Osuntokun (1971) have reported on rates of large vessel disease in Nigerian diabetics. Severe hyperglycemia was common, but rates of large vessel disease were very much lower than in the U.S. black diabetic population.

In the publication edited by Tsuji and Wada (1970), several reports document the very low rates of coronary diabetic disease in many Asian populations. Evidence from several sources indicates that the immunity enjoyed by these people is not mainly the result of racial factors. For example, relatively affluent Indian diabetic patients residing in Africa have very high rates of large vessel disease, while in certain parts of India, vascular disease is relatively uncommon in diabetic persons. The possible role of nutritional

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factors in determining immunity or susceptibility to large vessel disease in diabetics has been reviewed by West (1972, 1973, and 1975). A report in press by Inglefinger et al. summarizes the experience of the NIH group studying diabetes and its manifestations in the Pima Indians. Despite the extreme frequency of hyperglycemia, rates of coronary disease seem to be lower in the entire population than in other elements of the U.S. population. Even the Pima diabetic population seems to have a rate of coronary disease similar to or slightly below that of the general population of the United States (Bennett, 1973).

Robertson and Strong (1968) summarized studies of the effect of diabetes on coronary atherosclerosis in 14 populations living under widely different conditions. In some of these localities, the number of specimens was very small, and other problems also made interpretation difficult. The data are nevertheless informative and impressive. In all societies, diabetes seems to be associated with some degree of enhancement of rates of atherosclerosis. Even so, diabetic persons in some societies exhibited much higher levels of arterial disease than did those in other population groups. Furthermore, in some societies, arteries of nondiabetics were more diseased than those of diabetic persons in other populations.

Because hyperglycemia tends to produce hypertriglyceridemia, the possibility has been considered that the increased levels of coronary disease in diabetics might be attributable in part to their higher triglyceride levels. Data of Santen (1972) in groups of diabetics with and without vascular disease were compatible with this possibility. There is a considerable body of evidence for and against a role for hypertriglyceridemia in the enhancement of atherosclerosis in nondiabetics (Albrink, 1973, and Stamler, 1973). Kannel (1975) and Garcia (1974) reported data from the Framingham studies suggesting that very little of the increased rate of large vessel disease in diabetes was explained by factors associated with hyperglycemia, including hypertriglyceridemia.

On the basis of their studies of risk factors for coronary heart disease in Hawaiian and Japanese males of Hawaii, Chung et al. (1969) were unable to detect "any association between the level of triglyceride and coronary heart disease independent of the history of diabetes." Schonfeld and Kudzma (1973) investigated the status of glucose tolerance in 18 consecutive patients with type IV hyperlipoproteinemia. Impaired glucose tolerance was demonstrated in 50%. Although there is considerable literature on the relationships between adiposity, glucose intolerance, and hyperglycemia, these interrelationships are still incompletely understood. Few data are available from representative samples of individuals in whom all three factors were measured. Even

when this has been done, the numbers are sometimes suboptimal. For example, the numbers of diabetics in both Framingham and Tecumseh are small, and glucose tolerance was not measured in Framingham. Shapiro et al. (1973) measured serum lipids in both white and Bantu diabetic patients of South Africa. Bantu diabetics had far less large vessel disease than the white diabetics, but triglyceride levels were not significantly different in the two races. The Bantu diabetics had serum cholesterol levels that were substantially lower.

Levels of large vessel disease in population groups seem to relate rather consistently with levels of serum cholesterol. There are, however, a few apparent exceptions of some degree. For instance, large vessel disease seems to be quite uncommon in the Navajo diabetic population, although some observers have reported serum cholesterol levels in the general population of Navajos which approach those in the U.S. white population. In a study of Hadden et al. (1973), risk factors for myocardial infarction were compared in maturity-onset diabetes. In these studies, initial blood glucose and initial weight were only weakly positive as risk factors (not statistically significant), while cholesterol and diastolic blood pressure were strongly associated with risk of infarction.

Only a few data are available concerning the responses and the mortality rates of diabetics following the newer surgical procedures for improving the coronary circulation. A recent report of Verska and Walker (1975) compared outcome in 35 diabetic and 77 nondiabetic patients, finding relief of symptoms equally common in both groups. Operative mortality was 9% in diabetics and 4% in nondiabetics, but the small numbers must be kept in mind.

10) Pathology

The following table (Table 10) is a summary prepared by Knowles et al. showing the various degrees to which diabetes has influenced rates and amounts of coronary atherosclerosis as determined by studies of pathologists.

In diabetes, the papillary heart muscle also contains a high concentration of cholesterol and triglycerides (Alavaiko et al., 1973).

c. STROKE

Much of the above discussion concerning the increased rate of atherosclerosis in diabetics is also applicable to the circulation of the brain. Diabetic patients have more strokes than nondiabetics.

TABLE 10

PATHOLOGIC MANIFESTATION OF CORONARY DISEASE FREQUENCY
IN DIABETICS COMPARED TO CONTROLS TABLE OF KNOWLES
FORGARTY REPORT (In Press)

Author	Year	Group	Pathology	Age	No.	Percent	Ratio
Blotner (12)	1930	D	CAD	34–78	77	45	2.1
		ND		40–80	450	21	
Enklewitz (33)	1934	D	MI	50–69	74	31	1.9
		ND		50–69	520	16	
Nathanson (73)	1932	D	CAD	>50	74	53	6.6
		ND		>50	249	8	
Root (93)	1939	D	CAD	11–90	349	51	2.8
		ND		0–100	3400	18	
Hart (48)	1942	D	CAD	40+	193	46	1.6
		ND		40+	2250	29	
Starns 96)	1947	D	CAD	40+	50	75	2.0
		ND		40+	400	37	
Clawson (23)	1947	D	CAD	40–80	978	18	2.0
		ND		40–80	24923	9	
Goldenberg (42)	1958	D	MI	10–80	264	50	2.2
		ND		10–80	3206	23	
Feldman (39)	1954	D	CO	40–90	137	44	2.2
		ND				20	
Goodale (44)	1962	D	CO	40–80	65	62	1.7
		ND		40–80	445	37	

D – diabetic   CAD – coronary artery disease
ND – non-diabetic   MI – myocardial infarction
                            CO – coronary occlusion

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The degree of increased risk, however, has varied considerably among different populations and subpopulations. Kessler studied mortality in a very large group of diabetics. Although persons with diabetes had more strokes than age-matched nondiabetics, excessive mortality from stroke was only modest (20% higher than in nondiabetics), accounting for only a very small portion of the considerable excess in the rate of death of diabetics. It may be added, however, that rates of stroke in diabetic patients may be diminished by the high rate of coronary disease. They die of coronary disease before they have an opportunity to die of stroke.

1)   Stroke Risk and Diabetes

On the basis of his rather extensive studies in Sweden, Gronberg (1967) thought that rates of large vessel disease including stroke were not much higher in diabetic than in nondiabetic persons. In contrast, other observations in Sweden by Larsson (1967) suggested that rates of stroke were much higher in diabetics. Although the numbers of diabetic patients in the studies conducted in Tecumseh and Framingham were small, the increased rates of stroke in diabetics are impressive. The Stroke Risk Handbook of the American Heart Association, based on experiences in Framingham, reflects the increased risk of stroke in diabetes. Indeed, the degree of increase in risk of stroke was as great as the increase in risk of myocardial infarction.

Studies in Israel by Najenson et al. (1970, 1973) and by Lavy (1973) suggested that rates of stroke might be increased as much as threefold or fourfold in diabetes. The studies in Israel included both stroke rates and stroke mortality rates. In the study of Westlund in Oslo, death rates from stroke in diabetics were increased fourfold in subjects under 70, and twofold in those over 70. In this population, excessive rates of cardiac disease were much more important than the excessive rates of stroke in accounting for the total of excessive deaths in diabetes levels in the general population, but the excessive rate of stroke contributed very significantly to the excessive death rate in diabetic persons.

In the Health Interview Survey of the National Center for Health Statistics conducted in 1964-1965 on the characteristics of diabetic patients, 3.3% were found on the basis of the interview to have "vascular disease of the central nervous system," while 2.2% had "paralysis." In interpreting these data, it is important to keep in mind that persons in institutions were not included. Other data of the National Center reflect the high rates of stroke and diabetes in institutionalized persons. It also seems likely that incidence rates for stroke would

be considerably higher proportionately than prevalence rates. This is because survival is on the average short in patients with strokes.

Shafer et al. (1973) summarized reports from the literature concerning the frequency of clinical diabetes among patients with non-embolic cerebral infarction. Rates of diabetes in this group ranged from 2% to 28%, but the lowest figure from any U.S. population was 8%. Twenty percent was an average figure. In Shafer's group of black patients, 28% were known to have diabetes. Data are quite incomplete concerning the frequency distribution of glucose tolerance in representative samples of the universe of patients with various types of strokes. Toole et al. (1975) reported a rate of known diabetes in 28% of a series of 160 patients with transient ischemic attacks due to atherosclerosis of vessels supplying blood to the brain. Joslin's textbook (edited by Marble) gives an account of the causes of death in the very large group of diabetic patients who died between 1956 and 1968, and only 12% of the deaths were attributable to cerebral vascular disease.

2) Special Features of Cerebral Disease in Diabetic Patients

In diabetic patients, vascular disease of the brain differs qualitatively as well as quantitatively from that in nondiabetics. Vascular lesions typical of malignant hypertension are rare in diabetics. This and other special features of hypertension in diabetes have been recently well reviewed by Christlieb (1973). Large hemorrhages seem to be no more frequent in diabetics, and may be less frequent. In the huge autopsy series reported from Minneapolis by E. T. Bell, major hemorrhage was less common in diabetic persons than in nondiabetics in those under 60 years of age, and encephalomalacia more common in diabetics. Aronson reported in 1973 on examinations of brain vessels in 5,479 consecutive autopsies. In the 677 with known diabetes, there was no increase either in major cerebral artery occlusion or lethal infarction. Cerebral hemorrhage was less frequent in the diabetics. The diabetics had a striking increase in the number of small multiple lacunar lesions, typically in tissues serviced by the paramedian perforating arteries (pontine base, thalamus, and basal ganglia). Average brain weight, particularly in the elderly, was lower in diabetics. Diminished size was particularly evident in the infratentorial tissues. Aronson also noted in the diabetics the complete absence of the necrotizing small artery lesions of malignant hypertension.

In some series, the greater frequency of elevated blood pressure probably accounts in part for higher rates of stroke in diabetes. There is some evidence that rates of stroke are less strongly related to serum lipid levels than are other parts of the vascular system. For example, in Tecumseh there was no apparent relationship of serum

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cholesterol and risk of stroke. Two factors that increase blood
pressure levels in groups of diabetic patients are their greater
adiposity and the prevalence of glomerulosclerosis. The latter
factor is, of course, of greater importance in diabetes of long
duration. In some groups, however, blood pressure levels have not
been significantly higher in diabetics than in nondiabetics. This
includes, for example, the population studied by Gronberg (1967).

Schliack et al. (1973) reported the results of 3,254 autopsies
in diabetics of East Berlin. Cerebral vascular disease accounted for
11% of these deaths. It was interesting that rates of cerebral
vascular disease were higher in women (13%) than in men (9%). This
difference was not accounted for by higher rate of premature death
from cardiovascular disease in the men. Rates of death from cardio-
vascular diseases were even higher in the women (61%) than in the
men (52%).

Vernet et al. (1975) studied the effect of hypertension on
outcome in a group of 744 diabetic persons, mainly elderly females.
Hypertension developed in 172 after discovery of diabetes, and the
risk of stroke was strongly related to blood pressure.

More studies are needed in diabetes concerning risk factors
of stroke and their interrelationships.

d. GANGRENE AND OTHER MANIFESTATIONS OF ARTERIAL DISEASE OF THE LEGS

In diabetic persons, excessive rates of gangrene are even substan-
tially greater than the considerable excesses in rates of coronary and
cerebral vascular disease. Factors other than vascular disease, such as
neurologic pathology and increased susceptibility to infection, account
to some degree for the very high rates of gangrene in diabetic patients.
But the main factor is the marked increase in vascular disease in the
arterial system of the legs. This includes increased amounts of intimal
atherosclerosis and of medial sclerosis.

Langberg et al. reported in 1971 on diabetes mellitus mortality in
the United States for the period 1950-1967 (Publication No. 10 of Series
20 of the National Center for Health Statistics). In persons in whom
diabetes was mentioned on the death certificate as the underlying cause
of death, gangrene was also mentioned frequently, at a frequency 20
times greater than for persons dying of other causes. On the basis of
his huge autopsy series, which included 411 diabetics with atheroscle-
rotic gangrene, Bell concluded that risk of atherosclerotic gangrene was
increased about fortyfold in diabetics! These vascular lesions also

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are responsible for very high rates of other disabling conditions of the feet and legs in diabetic persons, including intermittent claudication, pain at rest, and ulcers and infections of the toes and feet.

1) Peripheral Vascular Disease and Glucose Tolerance

Data are far from satisfactory, but present evidence suggests that about half of amputations are the result of clinically evident diabetes. There is also some evidence that rates of vascular disease in the legs are increased in persons with occult diabetes. About one-third of the patients of Wahlberg (1968) with intermittent claudication had impaired glucose tolerance. It has even been suggested that rates may be increased in pre-diabetes. Present data are incomplete and conflicting in this regard. Results of Ferrier (1964) were negative on this.

2) Morbidity and Mortality

Another major cost of diabetes is the mortality and morbidity that attend amputation in diabetics. In various large series of amputations, operative and post-operative mortality averages 20% in diabetics and in some series has been as much as 34% with major amputation (Silverstein and Kadish, 1973). In most series, mortality of diabetic patients is higher with amputation than in nondiabetics. In others, this was not the case. In a series reported by Otteman and Stahlgren (1965), mortality was not greater in diabetic patients.

Gensler et al. (1961) reported a large number of surgical procedures attempting revascularization. Mortality in diabetic persons was 6.2%, while the operative mortality in nondiabetic patients was only 1.6%. Very diffuse disease was noted in 43% of nondiabetics and 75% of diabetics. Good results were achieved in 77% of nondiabetics and in only 54% of patients with diabetes.

The degree to which diabetes contributes to total rates of peripheral vascular disease seems dependent upon the rate of diabetes in the population and other factors. It is quite variable. In the study of Selvaag (1962) in Oslo, only 8% of males and 14.7% of females with atherosclerosis obliterans had known diabetes. Of the Australian amputees of Little (1973), only 23% had known diabetes. In contrast, 57% had diabetes in a series of amputees studied by Moore (1972). In the series of Silverstein, 65% of patients who had amputations had known diabetes, and 45% were known diabetics in the series of Cotton et al. (1971). On the basis of his huge autopsy series, Bell (1950) concluded that diabetes accounts for approximately half of atherosclerotic gangrene in men and about two-thirds in females (Minnesota).

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Gangrene is quite rare in patients less than 40 years of age. In Bell's studies of 411 cases of diabetic gangrene reported in 1950, only one was under 40. Oakley (1956) studied morbidity in 1,240 British diabetics under 40 years of age without observing a single case of occlusive arterial disease of the legs. The rate of occlusive disease was only 1.3% in diabetics 40-49 years of age. In contrast, 11% of diabetics over 69 years of age had occlusive disease in the legs. In 100 cases of diabetic gangrene, Kramer and Perilstein (1958) observed no cases under age 40 in their series of 100 with diabetic gangrene. These considerations suggest the need to concentrate prophylactic measures on patients over 40, particularly those over 50 years of age.

Survival is poor in those requiring amputation. In a series of Silbert reported in 1952, only 41% of 294 diabetic amputees survived five years. Thirty percent of these had a second amputation within three years. In five years, 51% had had a second amputation. Whitehouse et al. (1968) have also reported on the later life of the diabetic amputee and the fate of the second leg.

Several studies have measured rates of morbidity other than gangrene in the diabetic leg. Ridisch (1974) studied rates of peripheral vascular disease in a large clinic population of 1,600 patients, mostly Puerto Ricans of New York City. Manifestations of vascular disease of the legs were present in 37%. These rates of morbidity were considered to be more than seven times greater than the expected rate in nondiabetic men and more than 37 times greater than the expected rate in nondiabetic women.

In the general population of Tecumseh, peripheral pulses were found to be absent twice as frequently in those whose blood glucose values were in the upper quintile. In Swedes studied by Nillson (1967), 2.6% had absent peripheral pulses, while 9.9% of diabetics had absent pulses. X-ray evidence of severe calcification was present in 4.8%, but in diabetes of short duration, calcification was present in 8.7%. In diabetes of long duration, severe calcification was present in 17.9%. In the studies of Christiansen in Denmark, only 4% of subjects under 50 had calcification by X-ray of the vessels of the lower extremities. In contrast, age-matched diabetics had calcification more than seven times as frequently (31%). In the group of diabetics under 50, the prevalence of calcification was 11% in diabetes of short duration, and 53% in long duration.

In this study, there emerged also a strong relationship between calcification and morbidity, but more data are needed to establish the degree of the relationship here. The group of long-duration juvenile diabetics followed by Priscilla White also have very high rates of

calcification (1972). Of her patients with diabetes for more than 35 years, 90% had evidence of calcification. Ferrier (1964) found medial calcification 2.5 times more frequent in diabetics than in controls.

Some studies have found little difference in the <u>distribution</u> of occlusive disease in diabetics and nondiabetic persons (Conrad, 1967). Most available evidence, such as that reported by Strandness et al. (1964), suggests that diabetic patients have a peculiarly intensive occlusive process of the smaller vessels of the foot. Although it is possible that circulation is further impaired by lesions in the micro-vasculature, most evidence suggests that these lesions have little effect. Strandness (1974) presented evidence in this regard, and Ferrier (1967) reached the same conclusion. Studies by the latter suggested that medial sclerosis and intimal atherosclerosis of the leg and foot vessels are responsible for the ischemia rather than endothelial proliferation in the microvasculature. Neubauer (1971) found a positive correlation between calcification of the media and glucose tolerance in persons not previously known to be diabetic. There was no correlation in this group between glucose tolerance and intimal calcification.

The high rates of occlusive vascular disease in long-duration juvenile diabetics, in their fourth and fifth decades of life, suggest strongly a relationship of duration of hyperglycemia and pathology. These findings are also compatible with an association between degree of hyperglycemia and morbidity. Other studies have often failed to demonstrate any relationship between this morbidity and either dura-tion or severity of diabetes. The problems in interpreting evidence in this field have been discussed above under coronary disease. At present, epidemiologic evidence is quite inadequate to establish the importance of any risk factor in diabetic gangrene or related lesions. Risk factors that urgently deserve further study include duration and degree of hyperglycemia, serum lipid levels, smoking, present and previous adiposity, serum insulin levels, diet, blood pressure, microvascular disease, and others. In many societies, rates of gangrene are very low in diabetic persons (West, 1972), and most of the available evidence suggests that this immunity is not due primarily to racial factors. This indicates a great potentiality for preventive measures.

3) <u>High Cost of Leg Pathology</u>

The cost of these disabilities is huge. A single period of hospitalization for amputation averages about $4,000. Neither the incidence nor the prevalence of amputation is known for diabetics. In the report of Bauer et al. (1967) concerning the health interview study of the National Center for Health Statistics, it was found that 2.2% of diabetics had had an amputation and 1.4%

had had a major amputation. Moreover, it is evident that these figures greatly understate the frequency of amputation in diabetic patients. In this particular survey, for instance, persons who were institutionalized were not included. In this group, rates of amputation are very high. Life expectancy of amputees is rather short (see below); thus, the percentage of diabetic patients who require amputation during a lifetime is very much greater than the percentage of amputees at any given time. Since no satisfactory data were available, eight American specialists with great experience in the field were asked to guess at the percentage of diabetics who would require amputation at some time during their lives. These estimates ranged from 5% to 15%, averaging 10%. In many instances, disability produced by amputation is modest, but frequently it is great. The national cost of this type of disability is vast. Assuming that present trends continue, more than one million Americans alive today will eventually require amputation from diabetic gangrene. Cost of hospitalization alone would be $4 billion, at present prices. Few systematically collected data are available concerning the quality and quantity of rehabilitative services available to diabetic amputees. The clinical impression of a series of consultants was that services in most major centers were good, but such services left much to be desired in many communities. Care of amputees and potential amputees in nursing homes is a major national health problem. The book of Levin and O'Neal (1973) is an excellent source of information and bibliographic citation on the diabetic foot.

3. SUMMARY AND CONCLUSIONS

a. THIS IS A MASSIVE PROBLEM

In persons with known diabetes, large vessel disease accounts for about 75% of all deaths. The degree of excessive rates and amounts of large vessel disease varies considerably among the subelements of the total population of diabetic patients (by age, sex, duration of diabetes, etc.), but on the average, persons with diabetes are about twice as likely to have heart attacks or stroke, and the rate of gangrene in diabetes is more than five times that in the general population. Moreover, there is increasing evidence that these large vessel lesions are also more common in the huge population of persons with occult diabetes or mild impairment of glucose tolerance. For example, in the detailed studies of the population of Tecumseh (Michigan), the excessive rates were observed even in those whose blood glucose levels ranked as far down as the twentieth percentile of the general population. These and other data suggest that diabetes is among the most important of all risk factors for atherosclerosis in Americans. The cost of diabetic macrovascular disease includes the cost of death, disability,

and medical care. The cost of a single hospital admission during which amputation is performed averages approximately $4,000, and the cost may be even higher in those instances where a limb can be saved through angioplasty. The number of diabetics who require regular care for heart conditions probably exceeds one million. When all of these costs of diabetic macrovascular diseases are combined, they must be measured in billions per annum. Diabetic large vessel disease constitutes one of the four most important and costly health problems in the United States.

b. CURRENT INFORMATION IS INADEQUATE

It is quite clear that this is a massive problem warranting highest national priority. On the other hand, more data are needed in order to develop strategies of attack that will have greatest effectiveness in relation to costs. We know, for example, that amputation is required with distressing frequency. But we do not know what percentage of diabetic patients require amputation, and our knowledge concerning the epidemiology of gangrene is inadequate. More information is needed on the prevalence, incidence, cost, and disability attributable to the various types of diabetic large vessel disease. Also, more knowledge is urgently needed about the factors which enhance or protect diabetics from these lesions.

c. THESE LESIONS ARE PREVENTABLE

While present knowledge is incomplete, it is quite clear that these lesions are not inevitable. Although atherosclerosis is more common in diabetics of all societies than in the general populations of these societies, in many populations of diabetics, rates of macrovascular disease are far less than in the diabetic population of the United States. Recent observations suggest strongly that the low rates are not mainly the result of genetic or racial factors. Rather, it appears that environmental factors such as diet account for most of this very fortunate immunity to the ravages of macrovascular disease. It is also of considerable importance to note that many American diabetic patients of all races escape these lesions. And even in the United States, there are certain subpopulations of diabetics with low rates of macrovascular disease. This includes, for example, the Pima and the Navajo Indians. The extent to which this immunity is genetic or environmental is unknown. Further studies of these special populations and subpopulations would yield important clues concerning the cause and prevention of these lesions.

d. RESEARCH: NEEDS, POTENTIALITIES, PRIORITIES, AND COSTS

The importance of these problems fully justifies an allocation of roughly 5% of the total national effort in research, i.e., about $100 million per annum. Much of this should be invested in basic and clinical research. Needs for these kinds of studies will be outlined in other parts of the Diabetes Commission report. This section will be concerned with only one aspect of the research attack. For the most part, the kinds of research required in gaining insight concerning the scope and impact of these problems are epidemiologic in character. Such epidemiologic studies would have several functions. One would simply be to assess more fully the costs of the various elements of this problem such as stroke, gangrene, coronary disease, etc. This would help in arriving at a priority for both the attack on the whole problem of macrovascular disease and the various components of the problem. However, studies of this kind would surely yield as by-products information leading to a better understanding of the characteristics of these problems. For example, systematic study of the problem of gangrene would provide useful information on which elements of the diabetic population have greatest need for intensive prophylactic foot care.

Another important function of epidemiologic studies is to provide clues to the basic and clinical investigators concerning which lines of investigations are most likely to be productive. For example, if epidemiologic studies show that levels of triglyceride in the serum have profound influence on rates of vascular disease in diabetes, the priority of basic and clinical investigation in this field would be raised. On the other hand, if well-designed epidemiologic studies show that triglyceride levels have little importance, a great deal of time and money might be saved on basic and clinical investigation in this field.

Probably the most important function of epidemiologic investigation is to point the way to the development of methods for preventing these lesions or diminishing their rate or extent. In practical terms, epidemiologic studies do not in themselves have potential for eradicating or preventing these lesions completely. Nor is it likely that any other kinds of research will wipe out the problem in a wholly decisive manner. On the other hand, it should be kept in mind that even modest reduction in the rates of this massive disease problem would confer benefits measurable in dollars at a rate of hundreds of millions yearly. Thus, diminishing the rate by 15% would be worth more than $150 million per year in every future year. Value over ten years: $1.5 billion.

Similar considerations have led to a very considerable national investment in other aspects of epidemiologic research in atherosclerosis. This effort was led by cardiologists rather than diabetologists. For

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this and other reasons, very little attention was at first given to diabetes and hyperglycemia in the course of these investigations. Diabetes, the quiet killer, was for the most part ignored in these studies. However, increasing recognition of the importance of hyperglycemia has more recently led several of these investigators to focus attention on diabetes in such studies. Nevertheless, the national effort in this latter field is still far short of the importance of the problem. There are several reasons for this. Until quite recently, scientists with competence in diabetes only rarely had interest or competence in epidemiology. No clearly identifiable source of funds had been earmarked for epidemiologic studies in diabetes or in diabetic macrovascular disease. Leaders in the field of the epidemiology of atherosclerosis were cardiologists who, although open-minded, were inclined to concentrate on those factors with which they have been traditionally concerned. Another deterrent has been the rather considerable cost of epidemiologic studies. An estimate of present expenditures in this field would be very difficult to make because of problems of definition. For example, some would consider the studies of the University Group Diabetes Program as a "clinical investigation," while others would consider this an epidemiologic enterprise. Although this latter study has considerable potential as a method for making epidemiologic observations, it was conceived primarily as a clinical trial, and, therefore, was not included in our generalizations concerning present levels of financing for epidemiologic research in diabetic macrovascular disease. At present there are only very few epidemiologic studies designed primarily to gain new information on diabetic macrovascular disease. In our more specific recommendations, we point out the need for both independent epidemiologic studies of diabetic macrovascular disease and the incorporation of more extensive data collection relating to diabetes as part of broader investigations of the epidemiology of macrovascular disease, such as in the studies in Framingham, Hawaii, Puerto Rico, the Lipid Research Centers, the Multiple Risk Factor projects, and others.

e. HOW MUCH WILL IT COST?

The rate of increase of investments in epidemiologic studies of diabetic macrovascular disease will depend on several factors. These will include the competing claims of other research approaches, limitations of total money and resources for research in diabetes and in vascular diseases, the logistical problems involved in mounting new studies, limitations of manpower, etc. At present, limitations of funds are considerably greater than limitations of manpower. One of the advantages of having an identifiable source of funding for this type of research, even if it is modest in magnitude, would be the effect on the recruitment of scientific manpower. One of the problems in recruiting scientists for long-range work in this field has been that

potential sources of funding have been less clearly identifiable than in other fields. One possibility for the mitigation of this problem would be the development of a division or branch or program in this field, perhaps as a joint enterprise of the two National Institutes most concerned (NIAMDD and NHLI). Funding at a level of about $20 million per year would be fully justified considering the importance of the problem and the potentialities of the epidemiologic approach. Taking into account, however, all aspects of the present situation, a more modest beginning would be appropriate. This might include an outlay of approximately $4 million in Year One, $7 million in Year Two, and $10 million in Year Three. These figures would assume that total expenditures for all research in this field, (diabetic macrovascular disease) including basic and clinical research as well as epidemiologic studies, would require a much larger budget. Assuming a total budget in Year Three for all diabetes-related research of approximately $150 million, about one-third of this might be appropriately invested in research on macrovascular disease ($50 million). Assuming that 80% of the $50 million per annum were spent on basic and clinical studies in this field, this would leave 20% or approximately $10 million for epidemiologic research in macrovascular disease. It would be, of course, appropriate and efficient to combine some of the epidemiologic studies in diabetic macrovascular disease with studies on other aspects of diabetes, including, for example, genetics, adiposity, micro-angiopathy, and other clinical aspects. Assuming a total research budget of $150 million per year for all diabetes programs and projects, about 15 to 20% might be appropriately invested in epidemiologic studies ($20-$20 million, about one-third of which would concern macrovascular disease). This latter figure could be expanded or contracted depending upon the breadth of definition of the term "epidemiology." The specific questions and deficits of knowledge that could be addressed by epidemio-logic methods are outlined below. Details will also be provided below concerning the specific methods to be employed in these investigations.

4. FUTURE DIRECTIONS

a. GOAL

The major goal of the suggestions outlined in this section of the report is to gain a better understanding of the scope, impact, and epidemiology of the macrovascular lesions of diabetes so that they may be prevented, mitigated, reversed, or more efficiently treated.

b. SPECIFIC OBJECTIVES

1) Gather more and better information

        In order to establish priorities and strategies in research,
public health, and clinical practice, more and better data are needed
on many aspects of this problem. There is need for a national diabetes
data system, one of the functions of which would be collection on a
continuing basis of information related to diabetic macrovascular
disease. This would be a cooperative but coordinated system having
Federal, private, state, institutional, and community inputs. These
collaborators would include specifically the National Center for Health
Statistics, NIH, CDC, other government agencies, state health depart-
ments, universities, the American Diabetes Association and its
affiliates, the World Health Organization, and other groups.

2) Epidemiologic research

        These enterprises would relate closely to the objective described
above, but they would be designed to study specific questions concerning
factors that enhance or protect against macrovascular disease. At what
level of glycemia does increased risk of macrovascular disease begin?
To what extent is elevation of the blood glucose an independent risk
factor in macrovascular disease, and to what extent is this strong
relationship the result of associated factors, such as elevation of
the serum triglyceride concentration? What factors enable certain
individuals and certain populations to escape the ravages of these
large vessel lesions? What is the relative importance of the following
factors in causing the increased rates of macrovascular disease observed
in diabetes: serum glucose concentration, obesity, serum insulin, serum
cholesterol, blood viscosity, blood coagulability, platelet-related
phenomena, ischemia of large vessel walls attributable to small vessel
lesions, genetic factors, duration and age of onset of diabetes, neuro-
pathic factors, smoking, dietary factors, exercise, blood pressure, serum
triglyceride concentration, levels of glucagon, etc?

c. APPROACHES

1) Improving the standardization of nomenclature, methods, proce-
dures, data collection, and reporting

        The value of the previous observations has been limited substan-
tially by inadequate and inconsistent definitions and lack of standardiza-
tion. Fortunately, it is not necessary to reach agreement on interpreta-
tions in order to develop some arbitrary definitions. Certain aspects

of this problem have been discussed in some detail by Kaplan and Feinstein (1973). Among the factors to be standardized or included in future studies are a working definition of diabetes and its sub-groups (including "fasting hyperglycemia," "abnormal glucose tolerance"); standard methodology or standard reporting with respect to the size of the glucose load, time of day, temporal relationship of loading to last feeding, size of loading dose, interval or intervals of time between loading dose and measurements of blood glucose concentration; standardization of measurements of plasma glucose levels; expressions of degree of overweight and adiposity; criteria and definitions con-cerning arterial disease of the legs and its subcomponents such as intermittent claudication, absence of peripheral pulses, presence, degree, and character of calcification by X-ray; and working definitions of "congestive failure," angina pectoris, myocardial infarction, etc.

Much work has already been done in this field that could be exploited in the formulation of future standardization. Much could be accomplished just by operational agreements about reporting certain kinds of results in the form of frequency distribution. Measures of this kind would permit maximum opportunities for pooling data from both past and future studies. A small percentage of future research funding could be used to support the further development of such definitions and standardizations.

2) Cross-sectional and prospective studies of representative samples

As indicated below, there are still some potentialities for answering important questions by using selected samples of diabetics in large clinics even though these samples may not be considered representa-tive. On the other hand, many of the important questions in this field require that studies be performed on more representative population samples. These samples would, in some cases, include certain age groups from the entire population (diabetic and nondiabetic). Certain kinds of studies might include only all diabetic patients, or a representative sample thereof from a general population. Some of these studies might concentrate on certain special elements of the representative sample of diabetic patients. This would include, for example, subjects with diagnosed diabetes, occult diabetes, subjects with fasting hyperglycemia, subjects with slightly abnormal glucose tolerance, and subjects whose glucose tolerance results lie at various other levels of frequency distribution curves.

These studies should include extension and expansion of studies in populations in which observations have previously been made -- for example, the populations in Framingham, Tecumseh, the Arizone Pimas, Sudbury, Honolulu, Chicago (Stamler), etc. Among the populations that might be studied or included are the previous, present, or past

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subjects examined or interviewed in the course of the surveys conducted by the National Center for Health Statistics. Many of the present population studies do not include enough persons with diabetes to answer certain of the more important scientific questions. This is because the many interrelated variables discussed above often require the development of many subcells. Study of several thousand diabetic patients may be required to answer some of the major questions. It will probably not be feasible to study an entire population of diabetics and nondiabetics in which there are as many as 3,000 with known diabetes. However, this kind of study could be done by recruiting and testing only a small subsample of those with no apparent diabetes in a large general population. Also, there are certain studies that would not require a control group of nondiabetics.

In Section b, immediately above, there is a list of risk factors and potential risk factors that would deserve study in such enterprises. One important need is to study further the interrelationships of these various factors. For example: To what extent is the relationship between hypertriglyceridemia and diabetes a function of the increased adiposity with which each is associated? To what degree do age and age of onset of diabetes influence the strength of association between level of glycemia and risk of developing stroke, heart disease, or occlusive vascular disease of the legs? Among the approaches that might be used in developing these population samples would be a registry of all diabetics in a community or region, or of certain subelements of the population of diabetics.

3) <u>Study of special population groups or population subgroups</u>

This would include populations of persons with diabetes in which rates of macrovascular disease are apparently low. The purpose of such studies would be to document the infrequency of such lesions and to identify and measure the factors with which this immunity is associated. Such populations include the Pima Indians in which rates of coronary disease seem to be low, other Indian tribes among whom the environmental and genetic factors differ considerably, populations abroad such as Japanese with diabetes, the various groups in Hawaii, etc. The World Health Organization has recently mounted a pilot project along these lines which deserves further encouragement and support. At present, the only United States populations participating in this are the Indian groups being studied by Bennett in Arizona and by West in Oklahoma. It would be desirable to add to this group of populations an American group of whites and of blacks.

Since age and age at onset of diabetes have important influences, it would be desirable to study further the natural history of macro-vascular disease in various subgroups of the general population of

diabetics. There is, for example, a substantial number of juvenile diabetics in the fourth and fifth decades of life who have neither obesity nor elevations of serum lipids. Careful evaluation of rates and characteristics of macrovascular disease in this subgroup would permit testing of a hypothesis that the association between hyper-glycemia and macrovascular disease is in this circumstance independent of obesity or elevated serum lipid levels. Other special groups deserving study are twins and other close relatives of known diabetics, including nondiabetic offspring of two diabetic parents. Among the control groups of interest may be included the nondiabetic spouses of persons with diabetes. The recruitment of this group is made easier by their natural interest in diabetes research. Their value as a control group relates to the fact that they are usually well matched with their diabetic spouses for factors such as age, social and economic status, ethnic group, environmental circumstances, levels of education, etc. Thus, matching of this kind permits a better opportunity to observe the effects of diabetes itself. Glucose tolerance declines in old age. Studies are needed to determine whether mild impairment without fasting hyperglycemia is attended in old age with increased risk of vascular lesions and to what degree.

Prevalence studies will often be elucidating, particularly when most of the relevant factors are measured (e.g., glucose, lipids, adiposity, vascular status, smoking, blood pressure, etc.). On the other hand, certain phenomena will be best evaluated by prospective studies of incidence. In some cases, only retrospective studies will be feasible, but with appropriate design, these can be helpful despite their limitations.

4) <u>Studies of the frequency of known and occult diabetes in repre-sentative samples of those with various kinds of macrovascular lesions</u>

It is particularly important here that representative samples be obtained. For instance, if the universe studied was a group of patients with amputation, rates of diabetes would be much higher if the institution in which the amputations were performed had an unusually high concentration of diabetic patients (e.g., a reknowned clinic for care of diabetes, etc.). Typical of such studies might be a study of the status including reported or measured glucose tolerance in all or a sample of amputees in a defined geographic region. Other specific entities that deserve further study with respect to their relationship to glucose tolerance include sudden death, congestive heart failure, cardiac enlargement, silent myocardial infarction, fatality rate and clinical characteristics of myocardial infarction, rate of heart disease

of occult etiology, various kinds of stroke, etc. In general, epidemiologic data on the relationship of diabetes to stroke and peripheral vascular disease are even more limited than data for coronary disease.

5) Studies using autopsy and death certificate data

Even though death certificates have limited reliability, and may at times be misleading, data from them do have some potential for providing clues. Particularly, this is so if the perusal of death certificate information is supplemented by studying in more detail all or a subsample of the deaths. Typical of such questions that might be pursued are: What percentage of those dying of acute myocardial infarction have known diabetes and how does this relate to age, sex, race, geographic location, urban-rural status, occupation, level of income, etc? Some of the same problems exist in using autopsy data. However, many of these problems can be mitigated by appropriate research strategies. Autopsy studies may be, on the one hand, part of prospective studies of outcome; while, on the other hand, they may be a starting point for retrospective studies of the characteristics of individuals autopsied -- such as presence or absence of known diabetes, age, sex, clinical and laboratory observations on the medical record, etc.

6) Clinical trials and intervention studies

Although these are in a sense epidemiologic in character, they have, in general, not been considered part of the scope of this committee. Suffice it to say here both their theoretical potential and their cost are great. Discussion of feasibility, cost, and benefits is beyond the scope of this element of the Report. Typical of such studies would be a design to determine whether or not lowering the blood glucose would, in itself, reduce rates and severity of macrovascular disease. This would be quite costly, but the importance of this question justifies a very considerable investment, if an appropriate design can be developed.

7) Administrative mechanisms for supporting epidemiologic work

As pointed out above, the development of resources and scientific manpower in this field has, to some degree, been limited by the lack of an identifiable and predictable source of long-term financing. In recent years, the most productive source of research in this field has been the unit established by NIAMDD for field studies in Arizona. The success of this group relates to several factors including the relatively predictable and stable source of financial support. This experience suggests that one of the possible strategies for encouraging

the development of more and better epidemiologic studies in this field would be the establishment of a few "centers" or "programs." This would not, of course, preclude channeling a major segment of funding through individual research grants on a competitive basis.

The epidemiologic research programs might be supported as one element of the existing or future diabetes research centers. Under this arrangement the Center would, perhaps, support only one or two epidemiology positions plus a small additional amount for core operations. Thus, the total core support and the continuing long-term commitment might be for amounts of approximately $100,000 per annum in this particular field. This epidemiologic work in diabetic macrovascular disease might be combined with other epidemiologic observations relating to diabetes, or observations on other diseases such as stroke and high blood pressure. A few scholars studying the epidemiology of diabetes and its macrovascular lesions would be expected to obtain most of the support of their research from additional appropriations outside the core budget. These would include local and national private sources, NIH grants, etc.

Such programs for epidemiologic research might also be established outside the multi-disciplinary diabetes research centers. Among many possibilities might be the establishment of a working consortium coordinated from the present NIH center in Phoenix. Collaborators in a Phoenix-centered program might include the University of Arizona and the University of Oklahoma (which is conducting epidemiologic studies in several Indian tribes of widely divergent geographic and genetic origins). Both the Arizona and Oklahoma studies are a part of the multi-national study on diabetic vascular disease sponsored by the World Health Organization. Thus, continuing liaison with the world-wide network might be accomplished through further development of ongoing enterprises in the southwestern United States. Another potential of such a consortium would be the study of the epidemiology of diabetes and its macrovascular lesions in other ethnic groups. For example, in Oklahoma one could study in the same communities representative samples of blacks and of whites as well as Indians. In certain sections of Oklahoma, the population is much less mobile than in the remainder of the United States. Certain resources and circumstances suggest considerable potential for a study of diabetes in Olmstead County, Minnesota. Physicians and scientists at the Mayo Clinic have already developed a considerable amount of data concerning the residents of this county.

There is a good potential for a comprehensive and detailed study of the scope, impact, and epidemiology of diabetes in a defined general population. This could be done either as a cross-sectional

study, a retrospective study, or a prospective study -- or perhaps one using all three approaches. Among the many possibilities here would be a better assessment of the cost of diabetes.

Some of the existing centers for diabetes research have potential for including epidemiologic elements. The excellent, ongoing work of Stamler at Northwestern on macrovascular epidemiology might be related to the University of Chicago Diabetes Research Center in the same community. The Diabetes Research Center in Seattle has special competence in macrovascular disease and could extend its studies to include epidemiologic observations. A Center or program for epidemiologic research would have excellent potential in Massachusetts. Resources there include the scientists of Harvard and the Joslin Clinic, the Framingham group, and the resources, special competence, and data of John O'Sullivan, who has followed population groups in Oxford and Sudbury. Among several other possibilities as sites for epidemiologic centers or programs is Atlanta (CDC, a huge diabetic clinic, and an exemplary clinical program at Emory University centered at Grady Hospital). This would be an excellent location for studying the epidemiology of diabetes in blacks. There have been extensive epidemiologic studies of vascular disease in nearby Evans County, Georgia. The diabetes center at Birmingham, Alabama, also has some resources that would be helpful in mounting a program of epidemiologic research in diabetes.

A consortium involving the excellent diabetes scientists at the University of Michigan and the investigators who have developed the Tecumseh studies would be potentially quite productive. Potentialities in Honolulu have been mentioned. Stanford University has special assets that could be useful in the development of further work in this field. Scientists at Case-Western Reserve (Miller, et al.) in Cleveland are already working with the NIH group in Phoenix. Basic scientists at the Diabetes Research Center in Chicago are collaborating with the University of Oklahoma group in studying in various ethnic groups the interrelationships among serum insulin levels, genetics, diabetes, adiposity, diet, and macrovascular disease.

Another possible site for another epidemiologic research program in this field would be Baltimore or Bethesda. Workers in this area include some of the participants in the University Group Diabetes Program, Andres and his associates at the Aging Research Center of HEW, the Rockville personnel of NCHS, and the NIH scientists.

In any such program, there would be great potential for gaining a better understanding of the genetics in diabetes. An allocation of $500,000 to $1 million yearly would finance core activities for several epidemiologic research programs which would then be in a position to obtain additional support through the several resources mentioned above.

5. THE HIGH PRIORITY AND FEASIBILITY OF PREVENTING DIABETES AND ITS COMPLICATIONS

a. THE ROLE OF EPIDEMIOLOGIC RESEARCH

Theoretically, prevention of most diabetes is feasible. This goal should be pursued vigorously using investments commensurate with the massive importance of the problem. <u>In some respects, prevention is preferable to cure</u>. For example, cure of diabetes would not make possible the reversal of blindness in most diabetics and would not prevent complications that are so frequent in undiagnosed diabetics such as coronary disease, ketosis, gangrene, etc. Moreover, the theoretical feasibility of prevention is well established.

Epidemiologic investigations have shown that rates of diabetes vary more than tenfold in different societies and that, for the most part, these differences are not primarily the result of genetic factors. Present evidence suggests strongly that if hyperglycemia were <u>prevented</u> in these populations, the vascular lesions would also be prevented. (This report summarizes much of this evidence.) Recent epidemiologic evidence suggests that a <u>substantial majority of diabetics would never have developed diabetes or its complications had they avoided obesity</u>. In a sense, <u>the main cause of diabetes is known</u>. <u>It is obesity</u>. <u>Even juvenile diabetes is strongly influenced by environment</u>. It is at least five times more common in Japan today than a generation ago.

<u>The macrovascular lesions of diabetes are preventable even in the presence of considerable hyperglycemia</u>. Why do some people and some societies escape coronary disease even in the presence of diabetes? Why do some diabetics escape disability for 40 years or more, while others develop serious or fatal complications in the early stages of diabetes? American black diabetics have, for example, about ten times as much coronary disease as black diabetics of South Africa or Nigeria.

The capabilities of epidemiologic research are several: (1) Their <u>main use is to identify and measure the factors that have potential in the prevention of diabetes and its complications</u>. This information has immediate <u>practical</u> application in the development of strategies and priorities of preventive measures. (2) Another purpose of epidemiologic research is to provide both positive and negative clues for basic and clinical scientists, to make this research more effectively targeted and productive. Epidemiologic evidence, for example, has led to an intensive study by basic scientists of obesity and lipid metabolism in diabetes. (3) Another use of epidemiologic work is the documentation of the magnitude and impact of the diabetes problem

and its various aspects, thereby establishing and justifying a national priority for diabetes research and control programs appropriate to its vast scope and impact.

Following is a list of some of the specific and urgent questions that require an intensified effort in epidemiologic research. The purpose of the list is to illustrate the very practical application of this approach to the prevention of diabetes and its complications. Even with much better information, there will remain a considerable disparity between what is theoretically applicable in prevention and what is feasible. On the other hand, the availability of better understanding will broaden the practical alternatives in developing prevention strategies.

b. <u>PRACTICAL IMPORTANCE AND CAPABILITIES OF EPIDEMIOLOGIC RESEARCH</u>

DIABETIC PERSONS NEED ANSWERS TO THE FOLLOWING QUESTIONS:

These answers are critical to the development of more effective preventive therapeutic measures to protect diabetics and potential diabetics from the current ravages of diabetes.

1) To what extent does mitigation of hyperglycemia protect against the development of complications (blindness, heart attacks, kidney failure, gangrene, strokes, diabetic coma, etc.)?

2) To what extent are vascular complications enhanced or ameliorated by other factors? Why do some diabetics escape these complications for many years while others rapidly develop serious or fatal manifestations? What is the importance of the following: obesity and leanness, serum cholesterol and triglycerides, blood pressure, smoking, serum insulin, dietary factors, exercise, type of treatment, etc?

3) To what degree is diabetes preventable? In what ways? To what extent is prevention and mitigation of obesity possible? What is the most cost-effective way of achieving this? Are there dietary factors (such as increased sugar or fat consumption) that influence risk of diabetes or its complications? Do present traditional diabetic diets accelerate rather than ameliorate diabetic vascular disease?

4) What methods and criteria are most effective in the diagnosis of diabetes?

5) At what level of glycemia does risk of diabetes complications begin? Does this vary with characteristics such as age?

6) To what extent and under what circumstances can treatment of early diabetes protect against progression, or reverse diabetes and its complications?

1. STATEMENT OF THE PROBLEM

Diabetic neuropathy is the state of abnormal function of peripheral nerve pathways found in the diabetic patient. Although presumed to be related to the diabetic state and more specifically to the presence of hypoglycemia, this relationship is far from proven. Almost any pathway -- somatic or autonomic, motor or sensory -- can be involved. The disturbed functions can be ones of increased or decreased activity, and the course can fluctuate or end in some disfunction or remission. The relationship of neuropathy to other aspects of the diabetic syndrome is not well understood and will be discussed to some degree in subsequent paragraphs.

The principal forms of diabetic neuropathy are shown in Table 11. Among the somatic neuropathies are those of foot drop and diabetic amyothrophy, seen in the more extensive and less specific neuropathies in the upper extremities. Among the visceral neuropathies, one finds the effect on eye, the gastro-intestinal tract, the genital-urinary tract, and the autonomic nervous system, as shown in the table. Great variation occurs among these forms of neuropathy, but the complete clinical description is outside of the scope of this report.

The problems of diabetic neuropathy have not been well studied. Danowski et al. examined 374 clinical patients and failed to find an ankle reflex in 30%, decreased vibratory sense in 44%, and painful neuropathy in 9%. (Danowski et al., 1966). Mayne (1965) evaluated 220 diabetic patients and 110 controlled subjects of comparable age and sex ratio and found similar symptoms and signs, although with considerably less frequency, in some instances. His findings have been summarized in Table 12.

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* Prepared by Dr. Max Ellenberg et al.

TABLE 11

PRINCIPAL FORMS OF DIABETIC NEUROPATHY

1. Somatic neuropathy
   Lower extremities
       Foot drop
       Diabetic amyotrophy
   Upper extremities

2. Visceral neuropathy
   Eye
       Extraocular muscle palsies
       Pupillary changes
   Gastrointestinal tract
       Esophageal neuropathy
       Gastroparesis diabeticorum
       Diabetic enteropathy
           Neurogenic vesical dip function
               The incipient neurogenic bladder
               Retrograde ejaculation
               Impotence
3. Neuropathic ulcer
4. Autonomic nervous system
       Orthostatic hypotension
       Anhidropsis
       Vasomotor inability

TABLE 12

COMPARATIVE EXAMINATION OF DIABETIC AND CONTROLLED
SUBJECTS FOR NEUROPATHIC SYMPTOMS

	Control (percent)	Diabetic (percent)	P
Pain, parasthesias, numbness, weakness	10	37	< 0.01
Impotence (men)	11	36	< 0.05
Diarrhea	2	7	< 0.05
Constipation	5	16	< 0.05
Cold feet	19	39	< 0.05
Burning feet	17	31	< 0.05
Absent ankle jerk	12	46	< 0.01
Absent ankle vibration	8	23	< 0.01

(from Mayne, 1965)

2. STATE OF THE ART

a. FEATURES OF DIABETIC NEUROPATHY

Diabetic neuropathy is controversial in its entire background and clinical presentation.

1) Etiology

Considerable difference of opinion still exists as to the effects of control and duration and the relationship of stress precipitant factors, as well as the possible relationship to secondary noxious factors superimposed on a presumably already damaged and vulnerable nervous system. A sharp division exists between those who support the theory of multiple causative mechanisms and those favoring a unitary hypothesis.

2) Pathology

There are established vascular and metabolic aspects to the pathology. For vascular, an involvement of the vasa nervorum has been shown as well as ischemic infarction, which relates to mononeuropathy and mononeuropathy multiplex. Under the metabolic heading, segmental demyelination and Schwann cell involvement have been demonstrated. In addition, posterior column and posterior root ganglia have been involved in some cases and presumably are related to the syndrome of "pseudo-diabetes tabetica." Finally, neuromuscular junction deficits have been defined. Electromicroscopic studies have indicated a primary fault in Schwann cell function suggestively involving the lipid metabolism of these cells. The basic difficulty arises from the persistent attempt to try to explain all pathologic and clinical aspects of the diabetic neuropathy on one basis. The point of the matter is that all the factors are operative under different circumstances. Each has to be properly evaluated and correctly categorized.

3) Pathogenesis

Like so many other features of diabetic neuropathy, pathogenesis remains remarkably elusive. Obviously there are vascular and metabolic aspects whose precise involvement has not been defined. The question of hyperglycemia and relationship to duration remains unresolved. In stress-precipitated neuropathies, there seems to be a direct relation-ship to metabolic factors. The presence of a neural growth factor has been recently demonstrated, with a definite influence in determining

the numbers of dendrites and the rate of growth of ganglia as well as peripheral nerve tissue. Further investigation is clearly indicated in this area because it may have a definite bearing on the diabetic neuropathic syndromes. It is of noteworthy interest that the neural growth factor is closely related chemically to insulin and metabolically acts very much like it in the nerve tissue.

4) Metabolic

The more recent developments have clearly pointed to a significant role of metabolic factors in the development of the diabetic neuropathy. Although pyrurate metabolism was the first to be so explored since it is involved in the diabetic syndrome, no correlation has been established between it and the occurrence of neuropathy. The sorbitol pathway has been shown to be involved in the development of neuropathy in the experimentally induced diabetes of animals.

Although the problems concerning the localization of polyol pathway activity within the peripheral nerve have not as yet been resolved, the available evidence is compatible with their existence within the Schwann cell. That polyol pathway activity within the nervous system is not restricted to the Schwann cell is indicated by the presence of aldose reductase in brain and of sorbitol and fructose in both brain and spinal cord.

Recent studies have demonstrated that the decrease in peripheral nerve myoinositol concentration which follows the induction of streptozotocin-diabetes in the rat can be prevented by careful regulation of hyperglycemia by means of multiple daily insulin injections, but cannot be prevented by less stringent insulin treatment regimens. Dietary myoinositol supplementation results in increases in both plasma and nerve myoinositol concentrations in rats; and when dietary myoinositol is provided in concentrations of 1% by weight to the streptozotocin-diabetic rat, restoration of sciatic motor nerve conduction velocity to normal is achieved without a significant influence upon the abnormally elevated sorbitol and fructose concentrations in the sciatic nerve. There is evidence that the polyol pathway is normally present and active in the mammalian peripheral nerve, and that its activity is influenced by the ambient glucose concentration. Increased polyol pathway activity resulting from hyperglycemia produces increased sorbitol, fructose, and water concentrations, and also decreased free myoinositol concentrations in the peripheral nerve. These alterations are associated with a decrease in nerve conduction velocity which can be prevented by correction of hyperglycemia through careful insulin administration, and which can be reversed by the restoration of nerve myoinositol concentrations to normal through dietary myoinositol supplementation.

The relationship between the biochemical abnormalities which have been found to occur in the peripheral nerves of animals with experimental diabetes and the pathogenesis of diabetic peripheral neuropathy is uncertain. As yet, no data are available concerning (1) the alterations in the concentrations of polyol pathway intermediates or myoinositol which occur in the peripheral nerves of human diabetics, (2) the influence of treatment with insulin or diet, or (3) the influence of dietary myoinositol supplementation upon the composition and function of human peripheral nerve.

One of the most promising and least explored areas is lipid metabolism in the nerves. Myelin, by dry weight, comprises 75% of nerve tissue. Nerve lipid metabolism is influenced by insulin. A chemical analysis has shown reduced levels of cholesterol, phosholipids, and cerebrosides in diabetic nerve. A decreased rate of fat metabolism in diabetic nerve fiber has been demonstrated. Insulin will increase by fivefold the incorporation of glucose to form nerve lipids. A decrease in myelin content in diabetic nerve tissue, comparable to that in aging, has also been demonstrated.

These observations suggest that insulin deficiency and/or hyperglycemia could result in both qualitative and quantitative abnormalities in lipid synthesis in the peripheral nerve of the animal with experimental diabetes. In addition, they indicate that the correction of the observed abnormalities in lipid synthesis cannot be achieved by intermittent administration of insulin, but require instead the restoration of normoglycemia. The relevance of these abnormalities in lipid synthesis to the pathogenesis of human diabetic neuropathy is still uncertain. All these features point strongly to the necessary and indicated attack on the lipid aspect of diabetic nerve in the attempt to further elucidate the mechanisms of diabetic neuropathy.

Further work is required to establish the exact biochemical abnormalities in nerve lipid and indeed in other components of the nerve. Despite some discrepancies in results -- and important differences between young and old animals and early and late disease -- it does seem that in the myelin of diabetic nerve, fatty acid synthesis is impaired, with the consequence of reduced levels of lipids and altered patterns of lipid composition.

A recently suggested approach involves the study of orthograde axoplasmic flow. The transport of choline esterase and choline acetylase was significantly reduced in untreated streptozotocin diabetic rats but eliminated by insulin treatment. This approach opens an entirely different investigative area.

5) Electrophysiological Changes

From the numerous studies of nerve conduction in diabetic subjects, it is clear that abnormalities of sensory nerve conduction are the most consistent subclinical alteration, indicating that sensory fibers are usually the first to be affected. Motor conduction velocity too may be reduced in patients without clinical neuropathy, but the degree of reduction is greater when neuropathy is overt. Reduced nerve conduction velocity has also been demonstrated in alloxanized diabetic animals.

The main explanation for the reduction in nerve conduction velocity is likely to be the occurrence of segmental demyelination, although the selective loss of large nerve fibers and possible other factors may also be involved. However, an interesting and so far unexplained feature of peripheral nerve in the diabetic is that evoked, sensory action potentials are abnormally resistant to ischemia. The original suggestion that the inability to resynthesize is responsible has been discarded. The present theory postulates a periaxonal diffusion barrier which limits ionic exchange between that axon and the exterior. Impairment of this barrier could lead to an excessive efflux of K which would alternately lead to membrane depolarization and a conduction block. This is still unproven.

b. CLINICAL ASPECTS

Clinically the most common and disabling syndrome is peripheral neuropathy manifested by bilateral symmetrical involvement, primarily in the lower extremities. The most important symptom is pain which at times is so severe that it may require narcotics for relief. In such patients, even though the neuropathy may clear up, the constant threat and indeed occurrence of addiction is not unknown. A concerted attack on the need to prevent this type of severe painful neuropathy is evident. In the event that it does occur, the availability of therapeutic modalities to counteract it is definitely indicated. In addition, the amount of incapacitation and the economic impact of this complication are of alarming significance.

1) Relationship to Other Syndromes

The relationship to other syndromes is important. For example, although impotence and retrograde ejaculation in themselves are disturbing and all too frequent features of diabetic neuropathy, the secondary effects on infertility, sterility, and psychogenic overlay are indeed overwhelming.

The relationship of the neurogenic bladder to ascending pyelonephritis and the more frequent occurrence of urinary infection in the diabetic is of important potential prophylaxis.

Orthopedic, physical, and medical rehabilitation management can be advanced for the neuropathic foot ulcer. Neurogenic bladder must be relieved, and correcting if not preventive approaches developed for diarrhea, ataxia, and peripheral somatic neuronal syndromes.

Orthostatic hypotension is a result of compromising the barrorceptor reflexes in the carotid sinus and aortic arch and the chemiceptor reflexes. It is also related to a demonstrable lowering of the plasma renin, which in turn is related to catecholamines; but this is at best a contributory factor.

2)   Relationship to Diabetic Vascular Complications

The role of the autonomic nerve system in vascular complications must be revaluated and reascertained. Although we are familiar with many of the neurological manifestations as presented clinically by the autonomic nervous system involvement in diabetes, further exploration is needed on their possible, indeed, probable relationship to the development of vascular difficulties in the diabetic. Indeed, this may very well play a significant role in the marked increase in vascular complications that one sees in diabetes. Specifically, autonomic involvement can lead to orthostatic hypotension, which can of course have a significant deleterious effect on cerebral blood flow. Obviously, when this complication is at the advanced state of fainting and severe dizziness, it is readily appreciated; however, if one does routine studies, incidence of orthostatic hypotension is remarkably high. It could well play a significant role in the precipitation of cerebral vascular accidents which are known to account for 75% of all CVA's that do occur.

The markedly increased incidence of coronary artery disease in the diabetic person as compared to the nondiabetic is well known. Most of these patients have definite evidence of autonomic nerve involvement as shown by the Valsalva maneuver, the inability to regulate the heartbeat, and the absence of compensatory tachycardia when the blood pressure falls. In addition, there is an increased frequency of silent myocardial infarction in diabetes. These pathophysiological abnormalities have a definite relationship to cardiac function.

As for peripheral vascular disease, of every six amputations for gangrene, five are due to diabetes. While it is obvious that arteriosclerosis in the lower extremities and especially in the smaller arteries is much more common in diabetes, the fact remains

that many amputations are performed in diabetic patients even when there is adequate circulation. Actually, the chief difference between the diabetic foot and the nondiabetic foot is the presence of neuropathy in the former. The neurological involvement impedes the awareness of pain so that unperceived minor traumatic bruises and injuries occur, leading to secondary infection which serves as the coup de gras. There is no question that the ability to prevent or control diabetic peripheral neuropathy would be a tremendous boon to the diabetic population from the point of view of saving feet.

3) <u>Sex</u>

There is little, if any, sex difference in the frequency of diabetic neuropathy.

4) <u>Age</u>

All diabetic neuropathy is more commonly associated with adult maturity-onset diabetes. However, it is becoming increasingly evident that the juvenile diabetic is also at risk. For example, at the very onset of juvenile diabetes, electro-physiological measurements show, almost invariably, impairment of nerve conduction velocity as well as early involvement of some of the manifestations of sensory neuropathy. More recently, there has been demonstrated an early form of neurogenic bladder in diabetic persons. And, of course, as the duration of the disease proceeds in the juvenile, he is progressively more likely to develop diabetic neuropathy.

5) <u>Neural Regulation of Carbohydrate Metabolism</u>

Morphological recognition of neural elements in and around the pancreatic islets is credited to the discoverer of the islet, Paul Langerhans himself, in 1869. The neural fibers in the islets are unmyelinated; some exhibit positive acetylcholinesterase reaction, and others show significant uptake of tritium labeled noradrenalin, suggesting that both the adrenergic and the cholinergic subdivisions of the autonomic nervous system are represented.

Accordingly, insulin secretion from the B cells of the pancreatic islets is under the influence of the cholinergic (parasympathetic) as well as both alpha and beta adrenergic (sympathetic) neural impulses. Stimulation of the vagus (parasympathetic) nerves supplying the pancreas results in an increase of insulin secretion that can be blocked with atropin. In vivo administration of parasympathicomimetic (cholinergic) agents also elicits insulin secretion that can be blocked by parasympathetic inhibitor drugs.

c. <u>FUTURE DIRECTIONS AND APPROACHES</u>

There is strong evidence for neural influence upon glucagon secretion. A brief summary of current knowledge and research on the neural control of carbohydrate metabolism, and on the neural control of hormones relevant to carbohydrate metabolism, indicates this influence. The existence of neural mechanisms to increase as well as to decrease blood sugar levels has been shown. The rapidity of the neural influence on the metabolic process is impressive, suggesting that this form of regulation may be important in the minute-to-minute adjustment of the blood sugar level to the demands and supplies of glucose as it may arise during our everyday life. It appears that neural regulation may operate synergistically with or independently from other -- purely hormonal, or still other substrate dependent -- regulatory systems. The development of multiple regulatory systems to achieve a single purpose, optimal sugar concentration in the blood reflects the extreme biological importance of glucose homeostasis. The recent recognition of the important role of the CNS in this regulatory function opens up exciting new avenues for research into the pathomechanism, and perhaps the causes of important diseases of carbohydrate metabolism, such as diabetes mellitus, hypoglycemias, and hyperinsulinemic states -- including obesity, some types of hyperlipemias, and other related disorders.

Neuropathic involvement in diabetes is the least understood, most neglected, and possibly the most important underlying complication (or concomitant) of the diabetic syndrome. It is frequent, clinically important, and fundamentally significant with an untapped potential in the basic aspects of neuroendocrine and autonomic nerve relationships to physiological homeostasis and development of diabetic complications.

The need is pressing to educate and alert the clinician to the high incidence of diabetic neuropathy, its impact on the clinical picture, and its importance to the patient. At the same time, the need to undertake an aggressive continuing research program is paramount. This can only be accomplished by developing the interest and awareness of neurophysiologists, neurochemists, neuroendocrinologists, and neuropathologists. It carries with it the need to establish within existing facilities the expertise and the technical facilities for a concentrated drive.

1.   STATEMENT OF THE PROBLEM

For more than 100 years, it has been known that patients suffering from diabetes excrete ketones in their urine when the diabetes is in an uncontrolled state (Gerhardt, 1865); and, if untreated, they develop the life-threatening state of diabetic ketoacidosis (Hallervorden, 1879; Naunyn, 1900). Over many years, the term "diabetic coma" has been conventionally employed to designate a state of ketoacidosis in which the diabetic patient is in a precarious state of health, regard-less of the clinical level of sensorium (Bradley, 1971). In fact, increasing clinical experience indicates a lack of association between degree of acidemia and mental obtundation (Falop et al., 1975). Furthermore, diabetologists are becoming increasingly aware of the situations in which patients with otherwise relatively mild diabetes may deteriorate into an ominous syndrome of stupor or coma without significant ketoacidosis (hyperosmolar, nonketotic, hyperglycemia coma) (Arieff and Carroll, 1972), or into a syndrome of acidosis, predominantly due to accumulation of lactic acid rather than ketoacids (Tranquada et al., 1966; Oliva, 1970).

Of these three major causes of acidosis and/or coma in the diabetic, ketoacidosis still remains by far the most frequent. While the inci-dence and mortality due to this complication have both markedly declined since the insulin-era was ushered in (Marks, 1971), the preven-tion of ketoacidosis continues to be a "thorny problem" (Bradley, 1971). Because of ignorance, delay in recognition, or sheer negligence, deaths due to this complication may occur in patients with a fairly well-controlled diabetes. A clinical situation that should largely be preventable and, with today's facilities, successfully treatable, its continued occurrence may reflect upon the inadequacy of our system of health care delivery and patient education. In a recent extensive series of 482 episodes of ketoacidosis in 257 patients over a three-year period, as many as 13% terminated in death (Beigelman, 1971), while several other institutions throughout the country also continue to encounter a fatality rate of 3% to 10% (vide infra). The prognosis in hyperosmolar coma is even worse, with most published series reporting a mortality rate of approximately 50% (Arieff and Carroll, 1972).

The purpose of this report is to summarize the published and some unpublished (obtained through authoritative sources) data from various parts of U.S. on the current incidence of diabetic acidosis and/or coma and the mortality experience due to this problem.

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* An assessment of the problem in the United States, prepared by
Dr. O. P. Ganda and Dr. A. Marble.

2. IMPACT OF THE PROBLEM

The impact of the problem is far-reaching with significant socio-economic and health implications. A major fraction of patient population with ketoacidosis is young and in the most productive years of life. The acute deterioration in the metabolic state brought about by ketoacidosis and coma may precipitate severe neuropathy and trigger the onset and/or further progression of microvascular disease in relatively young patients (Bradley and Rees, 1963). It is generally agreed that at least two-thirds of all episodes of ketoacidosis and/or coma are avoidable, since they result from improper understanding about the disease and negligence. Even though the current mortality rates due to diabetic ketoacidosis and/or coma have been reduced to less than 10% in most series of reports, follow-up of patients recovering from such episodes has revealed an increasing trend toward ultimate death from nephropathy or cardiovascular insufficiency. Considerable disability results for the survivors, accounting for the socioeconomic impact on the individual's family and the society.

3. STATE OF THE ART

a. INTRODUCTION

A review of all available sources indicates no cumulative data on the incidence of ketoacidosis either in each U.S. hospital separately or in the entire country. Obtaining such data would be a formidable task since at present there is no strict system for collecting this information. Over the past several years, however, a nonfederal, nonprofit-making organization called the Commission on Professional and Hospital Activities (CPHA) in Ann Arbor, Michigan, has been assembling data on various diseases by requesting all short-term general hospitals of the country to submit an abstract of the information on every patient discharged. The data thus obtained from individual hospitals participating in this Professional Activity Study (PAS) are put together for each disease category and major subcategories. Pooled data from 1969 through 1973 are now available.

In 1969, a total of 6,155 hospitals throughout the country, constituting 17.5% of all U.S. hospitals, participated in this program. This represented a total of 838,014 hospital beds, or 27.8% of total discharges from U.S. hospitals. By 1973, the number of participating hospitals had increased to 6,422, or 24.5% of the total, representing a total of 924,894 beds or 35.6% of all discharges. The PAS information, then, reflects data on a fairly large sample of total patient population. The data are also subdivided according to the four geographical sections of the country. In terms of total hospital discharges from 1969 through 1973, the Eastern section

is represented by 29.6% to 34.2%, the Central by 34.3% to 46.9%, the Southern by 20.5% to 25.8%, and the Western by 25.4% to 35.0%.

We studied the total number of hospital discharges with diagnosis of diabetes mellitus and of those with diabetic acidosis or coma in the participating PAS hospitals of all sections of the country in an attempt to evaluate the incidence of acidosis or coma in various age groups in the five years and any possible changes in the incidence of this complication.

The data on the mortality in diabetes mellitus from this source are not yet available. However, some information was collected on the mortality rates from U.S. Vital Statistics publications and other published reports in the literature, and by personal communication with some of the major university hospitals. Information about some of the hospitals of the Greater Boston area was also obtained from the Massachusetts Hospital Association.

b. DATA ON INCIDENCE OF KETOACIDOSIS AND MORTALITY

1) Incidence (1969 through 1973)

Figure 1 presents the percentage of all diabetic patients admitted in ketoacidosis or coma in the participating PAS hospitals of the U.S. Over the five-year period of study, the percentage of all persons with diabetes presenting with this complication seems to be unchanged at approximately 14%. The analysis of different sections reveals the least frequency in the Central section (12%), followed by Eastern (14.5%), and Southern (16%) sections. The Western section, however, revealed a steady increase from 18.7% in 1969 to 22.5% in 1973.

Figure 2 shows the percentage of patients in different age-groups admitted in ketoacidosis or coma in all sections of the country. The greatest frequency of this complication was in the 0-19 age group, accounting for about 65% of all diabetic admissions, followed by approximately 40% in the 20-34 age group. The incidence in other age groups was as follows: 35-49 years, 13%; 50-64 years, 8%; and 65 years and older, 6%. Once again, no appreciable decline in the incidence was discernible over the 5-year period in any of the age-group categories. The progressive increase in the overall incidence seen in the Western section (Fig. 1) was found to be mainly due to steady increase in the 0-19 age group (69.9% in 1969 to 86.5% in 1973).
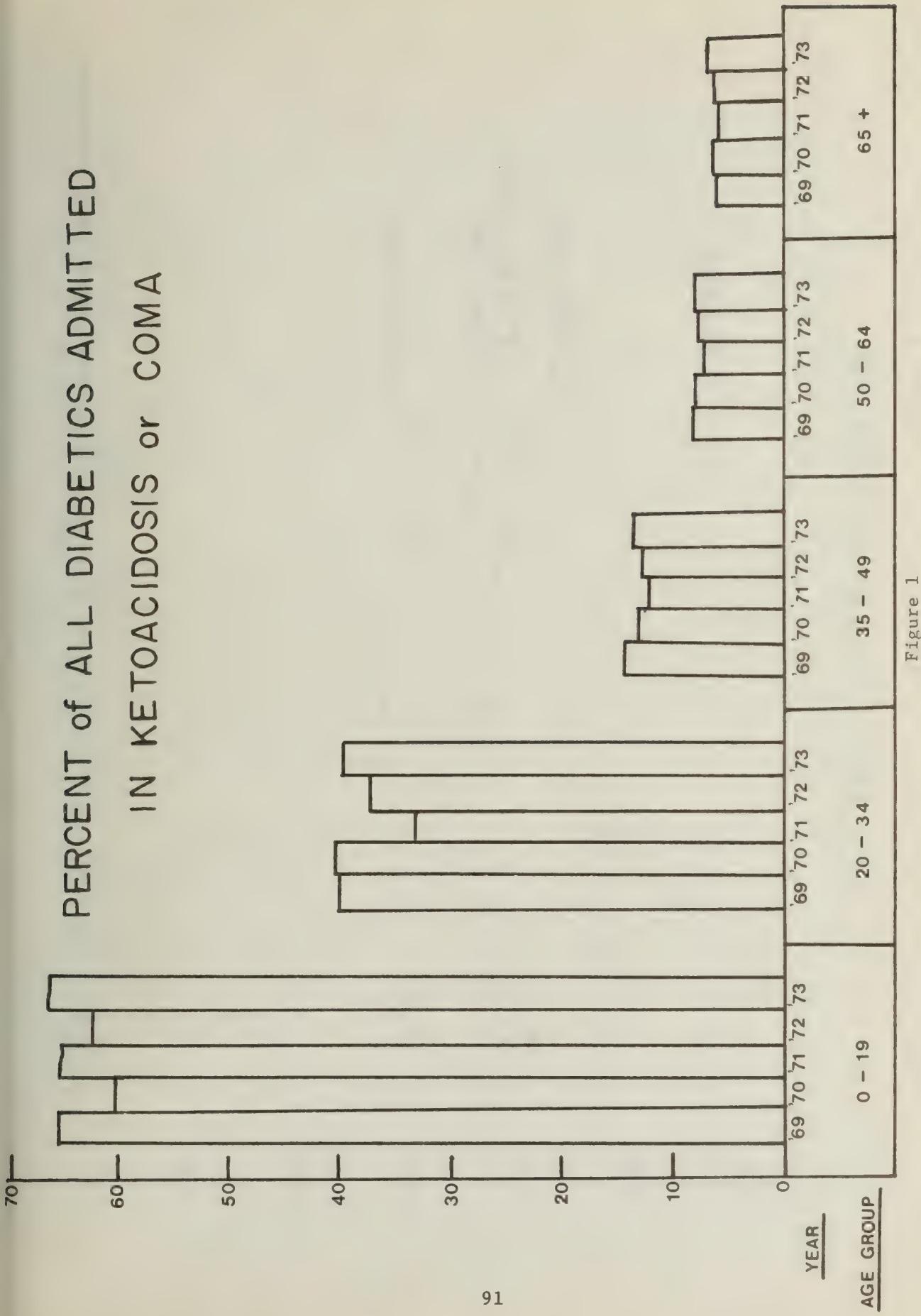
90

PERCENT of ALL DIABETICS ADMITTED IN KETOACIDOSIS or COMA

Figure 1

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PERCENT of ALL DIABETICS ADMITTED IN
KETOACIDOSIS or COMA

Western
Southern
TOTAL U.S.
Eastern
Central
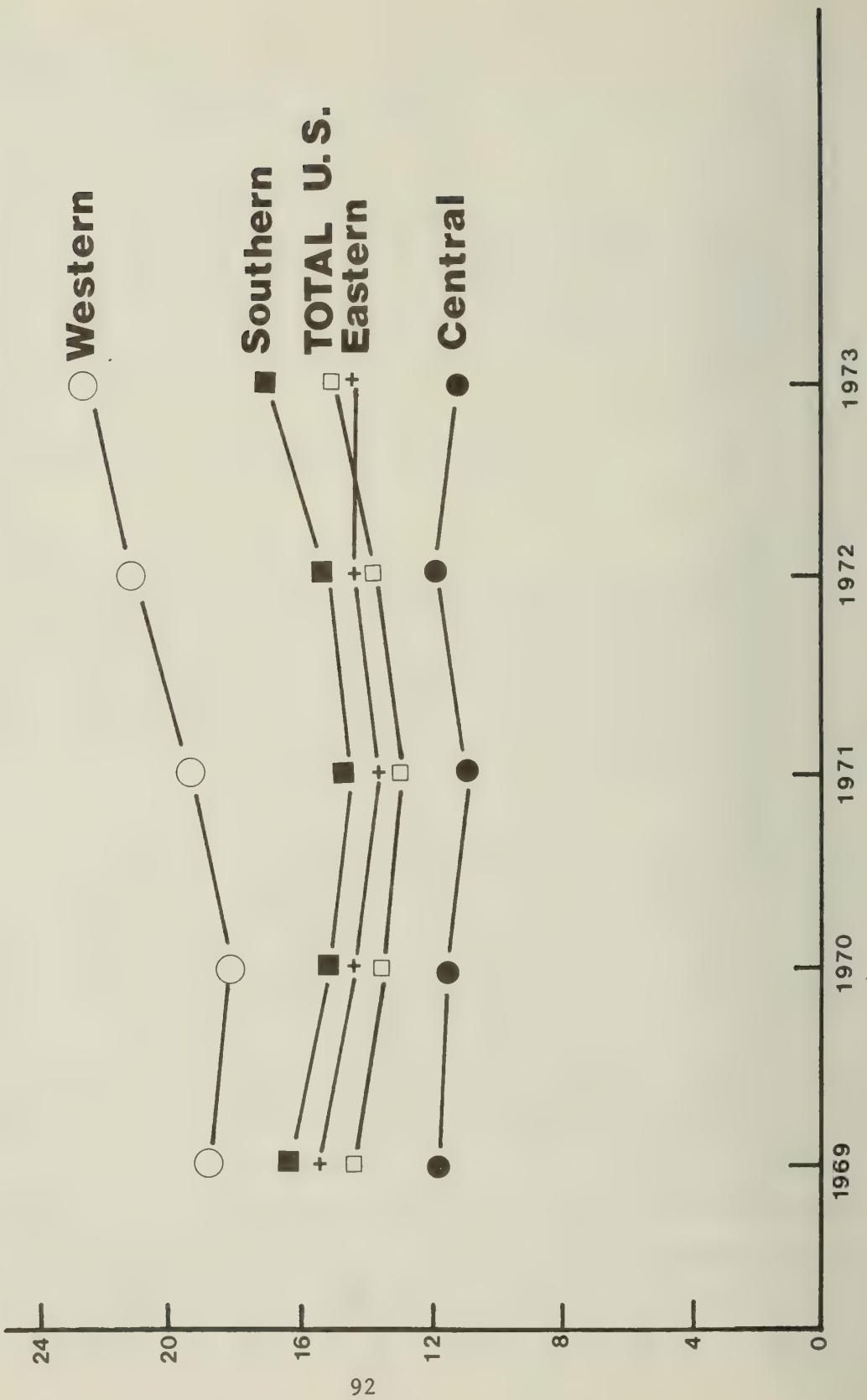
Figure 2

92

2) Mortality

Reports of U.S. Vital Statistics reveal currently approximately 38,000 deaths due to diabetes mellitus per year, or approximately 18.5 per 100,000 population. It must be understood that this death rate due to diabetes as registered in the current record systems is grossly inaccurate since only one disease is considered as the underlying cause of death. Patients dying from several other conditions where diabetes is a major contributing cause (e.g., cardiovascular) are, thus, not considered to have died from diabetes. In a recent study in Pennsylvania, eight per 100 patients whose death certificates did not mention diabetes did, in fact, have diabetes (Tokuhata et al., 1975). Thus, present mortality statistics obviously underestimate the signi- ficance of diabetes as a major health problem.

Figure 3 presents the death rates due to diabetes as recorded in U.S. Vital Statistics over many years. There was a gradual increase in the death rate due to diabetes from 16.2 per 100,000 in 1950 to 19.2 per 100,000 in 1968, stabilizing thereafter. Among all diabetic deaths, deaths due to ketoacidosis or coma have been analyzed since 1968. Through the most recent analysis of 1973, this complication continued to account for approximately 10% of all diabetic deaths.

Data on mortality in patients admitted with diagnosis of keto- acidosis or coma are not available for the entire country (see Table 13). While the mortality has been drastically reduced in the insulin-era, experience with large patient population at the Joslin Clinic revealed a 5.4% mortality in 204 episodes encountered over a seven-year period (1958-1965) (Bradley, 1971). In another extensive series of 482 episodes in 257 patients reported from Los Angeles (1965-68), the mortality was 13% (Biegelman, 1971). We have obtained some information on the current experience at four major university hospitals of the Greater Boston area and several others from different parts of the country which indicate a mortality rate of up to 10% of all patients admitted in ketoacidosis and coma.

Cumulative data on mortality rate in patients admitted with hyperosmolar coma are scant. Most published reports have indicated a 50% mortality (Arieff and Carroll, 1972). Lactic acidosis is a relatively rare entity insofar as published data would suggest. However, an association with phenformin therapy, particularly in the elderly and in those with impaired renal function is being increasingly appreciated. Seventy-six cases of lactic acidosis in patients receiving phenformin have recently been reviewed from the English literature (Dembo et al., 1975).

DEATH RATES FOR DIABETES MELLITUS   (PER 100,000)
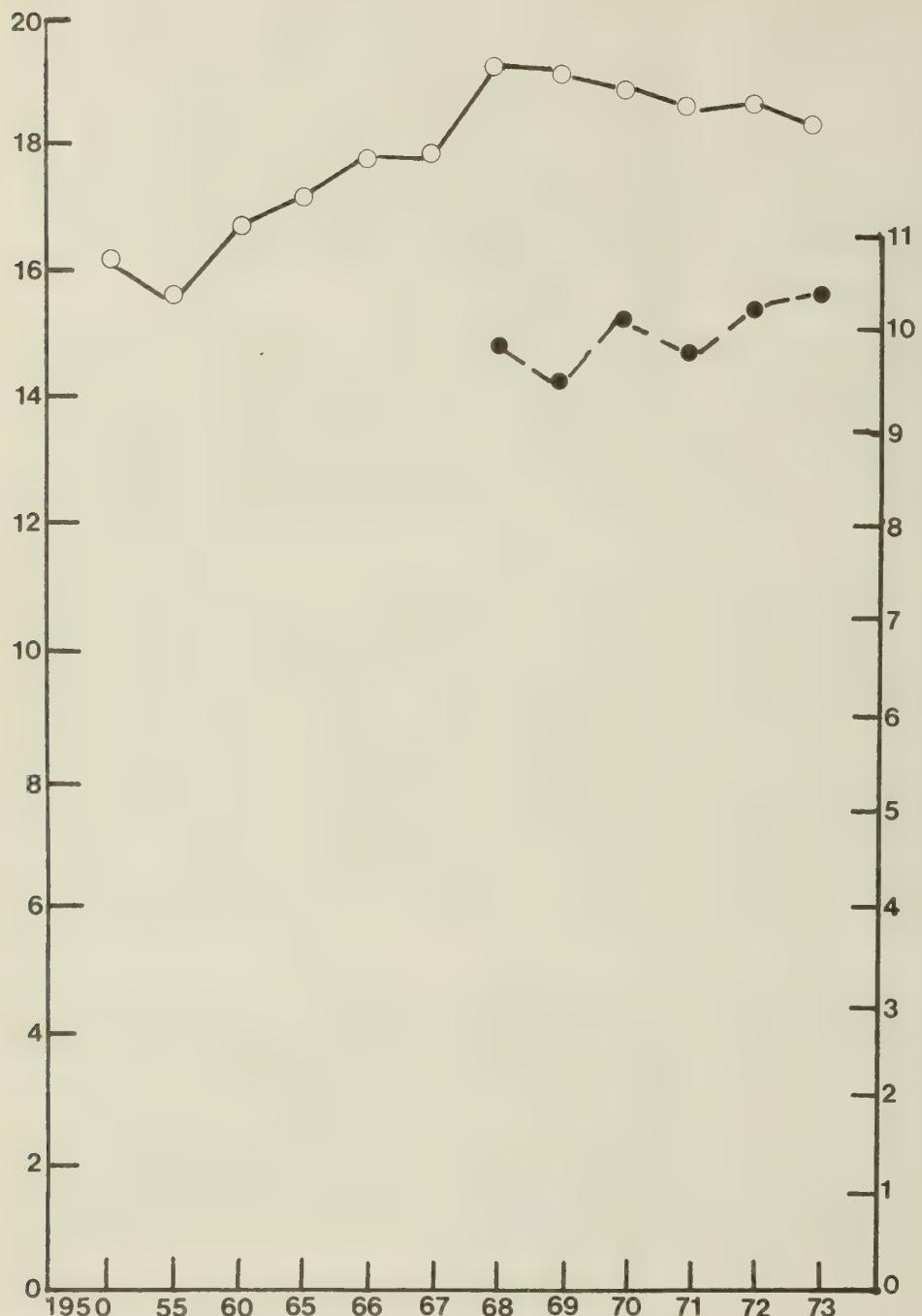
PERCENT OF ALL DEATHS WITH DIABETES MELLITUS
    DUE TO ACIDOSIS OR COMA

Figure 3

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TABLE 13

SUMMARY OF DATA REGARDING INCIDENCE AND MORTALITY IN DIABETIC KETOACIDOSIS,
HYPEROSMOLAR COMA AND LACTIC ACIDOSIS

Hospital	Period	Ketoacidosis or Coma			Hyperosmolar Coma			Lactic Acidosis		
		Total Admissions	Deaths	Percent Mortality	Total Admissions	Deaths	Percent Mortality	Total Admissions	Deaths	Percent Mortality
N. E. Deaconess, Boston	7/73-12/74	134	1	0.74	11	1	9.10	3	1	33.3
Peter Bent Brigham, Boston	1/72-6/75	48	5	10.40						
St. Elizabeth, Boston	7/71-7/75	37	5	13.50						
Boston City, Boston	4/71-7/75	309	24	7.76						
Mayo Clinic, Rochester, Minn.	1965-1972	149	23	15.44						
Medical College, Richmond, Va.	1974	40	1	2.50	12	1	8.33	60	19	31.67
St. Mary's, St. Louis, Mo.	1965-1974	227	12	5.30						
St. John's Mercy, St. Louis, Mo.	1969-1973	154	5	3.25						
Evanston, Chicago	1970-1974	203	?	?						
Northwestern Memorial, Chicago	1969-1974	191	?	?						
Henry Ford, Detroit	1970-1974	361	2	0.55						
Univ. of Colorado, Denver	7/73-6/74	45	1	2.22				26	5	19.23
Long Beach V.A., L.A.	1970-1974	247	46	18.62						
USC Med. Ctr., L.A.	1970-1974	459	28	6.10	149	35	23.42			
Mt. Sinai, N. Y.	1970-1974	138	6	4.35						

Note: These unpublished data were obtained by personal communication from information as nearly reliable as possible on short notice.

4. SUMMARY AND CONCLUSIONS

After our study of current magnitude of the problem of ketoacidosis and coma in patients with diabetes mellitus in the United States, the following conclusions appear warranted:

a. Diabetic ketoacidosis or coma continues to be responsible for 14% of all hospital admissions due to diabetes.

b. The incidence of ketoacidosis or coma throughout the country did not change over the five-year period from 1968 to 1973. In the Western section of the country, the incidence seems to have been on the increase from 1970 to 1973.

c. Diabetic ketoacidosis or coma currently accounts for 65% of all admissions due to diabetes in 0-19 age group and 40% of all admissions in 20-34 age group. The incidence in none of the age groups declined over the five-year period. The greatest increase over this period was seen in 0-19 age group in the Western section.

d. Ketoacidosis or coma is currently responsible for approximately 10% of all deaths in diabetic patients in U.S. hospitals.

e. Approximately 5% to 13% of ketoacidosis episodes still end fatally. The fatality rates in patients with hyperosmolar coma and lactic acidosis are not well reported but are probably much greater than those in ketoacidosis.

f. Current health education and delivery of care appear to be inadequate insofar as the prevention and treatment of acidosis are concerned.

5. FUTURE DIRECTIONS

a. GOAL

1) To prevent, insofar as possible, the occurrence of ketoacidosis or coma; or, at least, to ensure the early diagnosis of the acute complications of diabetes: ketoacidotic coma, hyperosmolar coma, and lactic acidosis.

2) If such complications occur, to recognize and treat them more effectively to reduce mortality to the minimum possible.

b. SPECIFIC OBJECTIVES

1) To include more instruction regarding diabetes and its compli-
cations in the curriculum of medical students, house staff, nurses,
and other health professionals in training.

2) To provide special training in diabetes from both investigational
and clinical standpoints for qualified workers by restoring and/or
continuing trainee programs, both research and clinical.

3) To provide adequate support for selected research projects
designed to answer problems related to the prevention and treatment
of the acute complications of diabetes.

4) To establish centers with facilities for research, training,
education, and patient care in diabetes at selected points in the
United States.

5) To develop both at national and local levels more effective
systems of data collection and retrieval regarding diabetes and its
complications, including those which form the subject of this report.

6) Through publications, radio, and television, to inform the
general public regarding diabetes and its complications.

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F. RECOMMENDATIONS: PROJECT SUMMARY SHEETS

Project Titles

1. Effect of Treatment on Morbidity in Diabetes

2. Study of Gangrene as a Health Problem in a Whole Community

3. Relationships of Glucose Tolerance, Adiposity, Serum Triglycerides, Vascular Disease, Genetics, Diet and Environment in a Whole Population or Representative Sample Thereof

4. World Health Organization Multi-national Study in Vascular Manifestations of Diabetes

5. Epidemiology of Adiposity in a Whole Community

PROJECT SUMMARY SHEET -- 1

PROJECT TITLE: EFFECT OF TREATMENT ON MORBIDITY IN DIABETES

OBJECTIVE: To determine the effect of metabolic control on the vascular
             complications of diabetic patients.

APPROACH TITLE:

    A long-term prospective multi-clinic trial on the effects of therapy
    on morbidity of diabetes.

DESCRIPTION OF PROJECT:

    Patients with insulin-dependent diabetes have early onset of degenera-
    tive complications leading frequently to early death.   Ten years
    after the onset of juvenile diabetes, Knowles found the following
    pathology: retinopathy in 64%, proteinuria in 33%, calcification
    in 27%, hypertension in 28%, neuropathy in 35%, and cataracts in 47%.

    If present methods of therapeutic intervention are useful, it should
    be possible to document this fact in a relatively brief period of
    10 years or less of observation.

    After careful explanation an informed consent patient will be
    randomly allocated to a routine treatment or a "tight control"
    treatment group. Multiple clinics having the capability of
    following between 100 and 150 patients on a long-term basis will
    be selected.

    Routine treatment will consist of therapy as it is now generally
    practiced in the community with dietary instruction and insulin
    therapy once or twice daily. This will probably be carried out
    under the total care of the primary physician with occasional
    consultation at the clinic in order to document progress. Patients
    assigned to "tight control" will have all known risk factors for
    vascular disease identified and eliminated or treated. This will
    include weight, cholesterol, and triglyceride normalization by
    dietary means, correction of existing hypertension, control of
    blood glucose by both dietary and insulin therapy. Insulin will
    be given twice or more times daily to control blood glucose
    below 160%mg two hours after the morning and mid-day meal.

Studies will be conducted of the major inpoints of retinopathy, coronary heart disease, peripheral vascular disease, nephropathy, neuropathy, blood pressure, and mortality.

Every attempt will be made to document the population screened for selected study patients so as to approach as closely as possible a 'total population' study.

KEY EVENTS CRITICAL TO THE
  SUCCESS OF THIS PROJECT:

1. Identification of an institute and principal investigators to provide continuity over 10 to 12 year period.
2. Assurance of long-term funding.
3. Identification of a loyal and stable population that can be followed for that period of time.
4. Assembly of a multi-disciplined and to some degree, inter-changeable team to measure and evaluate the progress of the research and the eventual outcome.

PRESENT STATUS:

There is a great deal of knowledge now available on the conduct of longitudinal studies and the experience of university diabetes programs is invaluable in establishing a study of this complexity. Extensive background in the technical complexities of controlling endpoint determinations has been developed.

INPUT REQUIRED:

No unique or unusual qualifications are required for this study that have not already been worked out. The most important single requirement is a well-disciplined control center for accumulation of data and for a modicum of results on an ongoing manner.

Cost for a total population of 3,000 patients studied over a 12-year period (two years' recruitment and 10 years of follow-up) would be approximately 1.3 million per year.

FORM OF RESULTS:

Results will be analyzed at six-month intervals for all endpoints to be certain that there is no significant difference between results of any two points of therapy. Evidence of significant difference between two points of therapy would be reason for conclusion of the study on the basis of the attainment of the research.

PROJECT SUMMARY SHEET -- 2

PROJECT TITLE: STUDY OF GANGRENE AS A HEALTH PROBLEM IN A WHOLE
                 COMMUNITY

OBJECTIVE: To learn more factors that inhibit or enhance risk of
             gangrene.

DESCRIPTION OF PROJECT:

    In a defined universe, all amputees during a three-year period
    would be studied together with a group of diabetics from the
    same universe matched for other characteristics such as age and
    duration of diabetes.

KEY EVENTS CRITICAL TO THE
  SUCCESS OF PROJECT:

    1. Find suitable population.
    2. Develop protocol.
    3. Obtain funding.
    4. Perform research and report results.

PRESENT STATUS:

    Very few data available.

FORM OF RESULTS:

    This would make possible better data on economic costs, morbidity
    rates and costs, and mortality rates. Also information useful
    in developing strategies for prevention. Risk factors studied
    would include degree and duration of hyperglycemia, serum lipids,
    type of therapy, smoking serum lipids, past and present adiposity,
    presence of other manifestations and complications of diabetes
    knowledge of prophylactic measures, etc.

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PROJECT SUMMARY SHEET -- 3

PROJECT TITLE: RELATIONSHIPS OF GLUCOSE TOLERANCE, ADIPOSITY, SERUM
                TRIGLYCERIDES, VASCULAR DISEASE, GENETICS, DIET, AND
                ENVIRONMENT IN A WHOLE POPULATION OR REPRESENTATIVE
                SAMPLE THEREOF.

OBJECTIVE: Learn more concerning inter-relationships of glucose
            intolerance, adiposity, triglyceridemia, and vascular
            disease.

KEY EVENTS CRITICAL TO THE
  SUCCESS OF PROJECT:

    1. Suitable population of sample of 3,000 in which adiposity
        and diabetes are common.
    2. Write detailed protocols.
    3. Obtain funding.
    4. Perform studies and publish results.

PRESENT STATUS:

    Present data are incomplete concerning these relationships.

INPUT REQUIRED AND FORM OF RESULTS:

    In order to examine the intensity and character of these relation-
    ships, one needs data on age adiposity, previous adiposity at
    birth, in childhood, adolescence, young adult life, lifetime
    maximum weight, anatomic distribution of adiposity, dietary
    constituents, characteristics of close relatives, also including
    past and present adiposity, triglycerides, glucose tolerance,
    age, status of vascular system (EGG, B.P., etc.,) serum insulin.
    The bases and chemical studies could be attached such as fat
    cell size on such samples, etc.

Note: This project would be incorporated as part of certain large
scale studies budgeted at 1.5 million/year. This element would cost
about $360,000.

PROJECT SUMMARY SHEET -- 4

PROJECT TITLE: WORLD HEALTH ORGANIZATION MULTI-NATIONAL STUDY IN
                 VASCULAR MANIFESTATIONS OF DIABETES.

OBJECTIVE: Gain better understanding of how to prevent vascular
            lesions of diabetes.

DESCRIPTION OF PROJECT:

    In 10 or more representative populations of diabetics, vascular
    lesions will be studied. Because these societies will differ
    widely, the study will identify the degree and causes of the
    expected differences in vascular lesions. It is proposed that
    funding be made available to facilitate participation of 2-3
    U.S. groups in this and 1-2 foreign populations in which
    vascular disease rates are low.

KEY EVENTS CRITICAL TO THE
  SUCCESS OF PROJECT:

    1. Design of protocol. (This has been done.)
    2. Organizational work. (Done.)
    3. Preliminary studies on some groups. (Done.)
    4. Broader base of funding, including funding of three sub-studies
        in the U.S.A. on black, white, and Indian groups.

PRESENT STATUS:

    See above.

INPUT REQUIRED:

    Identification of populations (Indian populations have been
    identified -- Arizona and Oklahoma) but it would be desirable
    to study a white or white and black population in America.

FORM OF RESULTS:

    Epidemiologic data applicable in better understanding, prevention,
    and therapy of vascular lesions.

PROJECT SUMMARY SHEET -- 5

PROJECT TITLE: EPIDEMIOLOGY OF ADIPOSITY IN A WHOLE COMMUNITY.
                (no such data are now available).

OBJECTIVE: Gain better understanding of causes and effects of obesity.

DESCRIPTION OF PROJECT:

    In a community of 3,000 plains Indians in Oklahoma, an epidemic of
    obesity will be studied. The opportunity is unique because:

    a) all medical records are centralized
    b) measurements of previous weights are available
    c) pilot observations have established feasibility

    Studies would include heights, weights, birth weights, of subjects,
    and close relatives. Weight over time, anatomic distribution of
    adiposity, glucose tolerance, attitudes about adiposity, diet, etc.,
    serum insulin and lipids, vascular status; basic studies on a
    sub-sample.

KEY EVENTS CRITICAL TO THE
  SUCCESS OF PROJECT:

    1. Establish feasibility (done)
        (community cooperation, etc.)
    2. Write detailed protocol
    3. Funding
    4. Gather and report data

PRESENT STATUS:

    Pilot studies only.

INPUT REQUIRED:

    Refinement of design and funding.

FORM OF RESULTS:

    Scientific reports leading to more effective methods for
    preventing obesity and its complications.

VI. Report of the

WORKGROUP ON

GENETICS

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

David L. Rimoin, Ph.D.

VI. THE REPORT OF THE WORKGROUP ON THE GENETICS OF DIABETES

A. BACKGROUND

The familial basis of diabetes mellitus has been firmly established by numerous studies all over the world. Despite the recognition of the importance of familial factors in the etiology of the disease, there is little agreement as to the basic nature of these factors. At one time or another, about every possible genetic (and sometimes nongenetic) mechanism has been suggested. The reasons for this unsatisfactory state of affairs are now fairly obvious. There appear to be all degrees of impairment in the ability to metabolize glucose in any properly studied population -- at what point in that continuum do we make the diagnosis diabetes mellitus? The basis for this impairment remains poorly defined despite the research efforts of the past. The disease may appear at any age, so that it is difficult to get a total picture of its impact in the family by a cross-sectional study. Because the disease is often undiagnosed prior to death, the "family history" given in all sincerity may be quite misleading, and studies utilizing family history data alone are unreliable.

Equally well-established is the importance of the environment in the frequency of the disease. For instance, Yemenite Jews at the time of their imigration to Israel had a very low frequency of diabetes; 25 years later, the frequency is similar to that of the other Israelis. Their genes have not changed in the meantime! Indeed, the life style of people all over the world is changing so rapidly that, given the environmental contribution to some types of diabetes mellitus, it is difficult to compare findings in successive generations.

Of all these impediments to definitive genetic studies, perhaps the most important has been the failure to understand the basic defect(s). Substantial progress in understanding the genetic basis of this disease cannot be expected until the nature of the primary defect(s) is better understood. In this connection, undoubtedly the most promising recent genetic development has been the growing realization that diabetes mellitus is not one disease, but a collection of diseases.

The initial convincing indication of this heterogeneity came from the association of diabetes mellitus with certain well-defined endocrine disorders, e.g., Cushing's disease or acromegaly, or as an accompanying feature of certain rare complex syndromes. All the remainder is usually called "idiopathic" diabetes mellitus. There is growing evidence that "idiopathic" diabetes is still genetically heterogeneous. This implies the existence of two or more fundamentally distinct entities all leading to carbohydrate intolerance or clinical diabetes. For instance, a form of

diabetes has been recognized in children, adolescents, or young adults who do not have the clinical form of juvenile-onset diabetes but who resemble clinically the maturity-onset type of diabetic. The familial aggregation of diabetes mellitus is much higher in these so-called MODY's (maturity-onset type of diabetes in the young) compared to other juvenile diabetics. Very recently, an international workshop conference on the genetics of diabetes mellitus focused on the complex question of heterogeneity. The results of this conference, which include a comprehensive survey of the literature on the genetics of diabetes mellitus up to February, 1975, will be published shortly (Creutzfeldt, Kobberling, Neel [eds.]: The Genetics of Diabetes Mellitus, Springer Verlag, Heidelberg, New York, 1975).*

Thus, although there is no question as to the familial aggregation of diabetes and to the importance of genetic factors in its etiology, it can be stated clearly that so-called diabetes mellitus is not a single, simply-inherited autosomal recessive trait, as has been widely publicized; and accurate genetic counseling presently cannot be given to diabetics. The practice of identifying "genetic prediabetics" solely on the basis of their being identical twins of diabetics or the offspring of two diabetic parents has proven to be erroneous, and genetic prediabetes can only be recognized retrospectively. A major problem in previous studies of the pathogenesis and genetics of diabetes has been the lack of ability to recognize the genetic heterogeneity, so that all forms of diabetes mellitus have been lumped together in the analyses. Certainly all future pathogenetic and genetic studies of diabetes must take this heterogeneity into account.

Further definition of the genetics of each specific type of diabetes will be dependent upon the definition of this heterogeneity and recognition of the basic defect in each disorder, so that specific markers for the individual genotype can be identified and utilized for genetic analysis.

B.   GENERAL GUIDELINES

Three general guidelines must be stressed in the performance of any genetic studies on diabetes.

First, it is apparent that further cross-sectional studies of the genetics of diabetes based on family history data or on the simple determination of carbohydrate intolerance are unlikely to be rewarding. On the other hand, it is of extreme importance to utilize prospective analysis in the studies to be outlined below in order to understand the

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*See the following bibliography for a list of the authors and titles of these papers.

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natural history of these disorders and to be able to distinguish varia-
bility in the expression of a single genetic trait from genetic hetero-
geneity. It is recognized that in the course of these genetic studies,
especially of the prospective type, certain ethical issues are apt to
arise. These ethical issues must be understood and appropriate safe-
guards introduced.

Second, large collaborative studies will be necessary to assemble
sufficient samples of individuals to be studied, especially in rare
genetic syndromes, rare clinical forms of diabetes, identical twins who
are both concordant and discordant for diabetes, etc. Furthermore,
collaborative efforts may be required to study multiple parameters in
each of the examples.

Third, the geneticist cannot operate in a vacuum and must serve as
part of a multidisciplinary team. His services should be utilized not
only to develop the protocol for epidemiological, biochemical, patho-
physiological, and other studies of diabetes, but also to perform
classical genetic analysis on the data provided by these studies.

C. OBJECTIVES

The ultimate objective in studying the genetics of diabetes is to be
able to provide accurate and specific medical prognostication, treat-
ment, prevention, and genetic counseling to each diabetic. To achieve
these goals, the primary objective must be the definition of the genetic
heterogeneity of diabetes, recognition of the different pathogenetic
mechanisms which might result in each form of diabetes, and ultimately
the ability to recognize the specific disease entity present in each
diabetic patient.

1. METHODS TO BE UTILIZED FOR ACHIEVING THIS OBJECTIVE INCLUDE:

a. Studies of markers apparently associated with diabetes mellitus,
e.g., the HLA (histocompatibility) system which may be one of the fac-
tors involved in a multifactorial etiology of diabetes, and could serve
as the model for study of other such factors.

b. A search for biochemical and hormonal heterogeneity in diabetes
in an attempt to define specific pathogenetic mechanisms and markers for
each form of the disease.

c. Studies into the pathogenesis of the glucose intolerance in the
many genetic syndromes associated with glucose intolerance and ascer-
tainment as to whether glucose intolerance exists in the carrier state
of certain of the recessive syndromes.

d.   Studies of diabetes mellitus in different ethnic groups, parti-
cularly those sharing a common environment and those in a stage of rapid
cultural transition, such as the American Indian. For example, utiliz-
ing standard criteria, in some Indian populations such as the Pima, 40%
of the population over 50 years of age have glucose intolerance.

e.   Twin studies -- especially of the co-twin control type which
involves identification of concordant and discordant monozygotic twins
at various ages in an attempt to identify different types of diabetes.

f.   Pedigree analysis involving the study of individual family units
utilizing all of the parameters listed below in an attempt to discern
specific patterns of inheritance.

g.   Population studies in order to ascertain the frequency of the
various primary abnormalities in diabetes within each population, data
which are required to test for specific modes of inheritance.

h.   Investigation into the various animal models of diabetes, espe-
cially to identify particular pathogenetic mechanisms in the animal and
stimulate a search for analogous processes in man.

2.   PARAMETERS TO BE STUDIED IN THE ABOVE INVESTIGATIONS, WHEN
APPROPRIATE:

a.   Clinical phenotype, e.g., insulin-dependent versus insulin-
independent, presence or absence of complications of the disease,
ketosis-prone versus ketosis-resistant forms, effect of therapy, etc.

3.   ONCE THIS INFORMATION IS GARNERED FOR EACH SPECIFIC FORM OF
DIABETES, THE FINAL OBJECTIVE WILL BE THE ABILITY TO:

a.   Identify individuals at risk for each specific disease.

b.   Offer accurate medical prognostication for the disorder.

c.   Utilize diet, drugs, or other environmental manipulation to al-
ter the clinical expression of the disease.

d.   Provide accurate genetic counseling.

However, when we are able to identify accurately individuals at risk
for diabetes and provide accurate genetic counseling, we must then study
the biological, psychological, and sociological impact of this informa-
tion on the individual and on the community at large.

D. MANPOWER NEEDS

It is apparent that most physicians in practice today have never received any education in medical genetics, that medical genetics is still not taught at all medical schools, and that diabetologists and other investigators in diabetes frequently have little knowledge of genetic principles. One of the major requirements for genetic manpower, therefore, is to train physicians, medical students, diabetologists, and basic investigators in the principles of medical genetics and how they may apply to diabetes.

Furthermore, since there is a generally recognized shortage of well-trained medical geneticists, an increased number of professional geneticists will be required to perform genetic analyses on the specific forms of diabetes once they are recognized and to provide genetic counseling for diabetics once this can be given.

E. BUDGET

It is impossible to place an accurate dollar figure on the budgetary needs to perform the above-mentioned studies. It must be stressed, however, that the long-term prospective and collaborative studies that are urgently needed in the investigation of diabetes are very expensive -- they could reasonably cost several million dollars annually -- and that there is presently no funding mechanism available for such studies. Such expensive prospective studies, of course, will include other areas such as the pathophysiology and epidemiology of diabetes.

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G. PROJECT SUMMARY SHEETS

PROJECT SUMMARY SHEET

PROJECT TITLE: ASCERTAIN THE EXISTENCE OF GLUCOSE INTOLERANCE IN THE
                 CARRIER STATE OF CERTAIN RECESSIVE SYNDROMES.

OBJECTIVE: To determine the pathogenesis of glucose intolerance.

APPROACH TITLE:

   The study of glucose intolerance in specific genetic syndromes
   associated with glucose intolerance.

DESCRIPTION OF PROJECT:

   Persons with certain genetic syndromes will be evaluated using the
   oral glucose tolerance tests to determine the presence or absence of
   glucose intolerance.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Identification of specific genetic syndromes.
   2. Well controlled oral glucose tolerance tests.
   3. Matching these results in similar group of patients without the
       genetic syndrome.

PRESENT STATUS:

   No current studies of this type are being done.

INPUT REQUIRED:

   Identification of appropriate patient groups.

FORM OF RESULTS:

   The identification of specific genetic syndromes associated with
   glucose intolerance.

PROJECT SUMMARY SHEET

PROJECT TITLE: TWIN STUDY OF THE CO-TWIN CONTROL TYPE.

OBJECTIVE: .   The study of diabetes mellitus in concordant and dis-
cordant monozygotic twins.

APPROACH TITLE:

Same

DESCRIPTION OF PROJECT:

Identify concordant and discordant monozygotic twins at various
ages in an attempt to identify different types of diabetes.

KEY EVENTS CRITICAL TO THE
SUCCESS OF PROJECT:

1. Identification of concordant and discordant monozygotic twins.
2. Perform FBS or OGTT when indicated.
3. Correlate this with age and other related factors.
4. Determine specific patterns diabetic development.

PRESENT STATUS:

A minimal amount of current knowledge is available in this field.

INPUT REQUIRED:

See above.

FORM OF RESULTS:

Results will be presented as cross sectional study of the subjects
involved.

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PROJECT SUMMARY SHEET

PROJECT TITLE: POPULATION STUDY TO DETERMINE THE FREQUENCY OF CERTAIN
PRIMARY ABNORMALITIES IN DIABETES WITHIN EACH POPULATION
GROUP.

OBJECTIVE: To ascertain the frequency of the various abnormalities
in diabetes.

APPROACH TITLE:

Population study to determine the frequency of certain primary
abnormalities in diabetes within each population group.

DESCRIPTION OF PROJECT:

Examine each population group and obtain the data required to test
specific modes of inheritance.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

1.   Identify population groups.
2.   Analysis of various abnormalities in diabetic population of
     each group.

PRESENT STATUS:

Several limited studies have been done in the past with inconclusive
results.

INPUT REQUIRED:

See above.

FORM OF RESULTS:

Results will be age, population and abnormality specific for
diabetes.

VII. Report of the

WORKGROUP ON

PREGNANCY

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

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VII.   REPORT OF THE WORKSHOP ON PREGNANCY
(Committee on Scope and Impact)

A.   STATEMENT OF THE PROBLEM AND ITS IMPACT

In spite of remarkable progress following the discovery of insulin, maternal deaths in the diabetic still outnumber those of the nondiabetic by an estimated factor of eight. The perinatal mortality rate in the diabetic remains five times that of the nondiabetic, even with good prenatal care, and two to three times greater still where such care is less than adequate. Maternal and neonatal morbidity is high. Current data indicate that the offspring of diabetic mothers have a high frequency of congenital malformations and exhibit many subsequent neurologic and conceptual deficits in addition to the increased risk of developing diabetes themselves.

The magnitude of the problem nationally is poorly documented, with estimates for the prevalence of overt diabetes in pregnancy varying from 1 in 1,000 to 1 in 200 pregnancies. More precise figures are available for gestational diabetes, but these are narrowly confined to one geographic area in a low socioeconomic setting. A transient, asymptomatic form of diabetes confined to pregnancy, gestational diabetes, occurs 23 in 1,000 pregnancies. Although part of the overall national problem, it has been widely neglected, largely because the discovery of gestational diabetes is dependent on the employment of an active screening program involving diagnostic glucose tolerance tests. Figures from the National Center for Health Statistics and the perinatal mortality rate make it possible to estimate the extent of this neglect. In 1973, an estimated 4,500 pregnancies resulted in perinatal deaths directly attributable to the effects of gestational diabetes. According to the results of a large, though preliminary, clinical trial, recognition of the condition and treatment with insulin and diet could have saved about half of these babies, and current monitoring techniques would undoubtedly reduce the remaining losses.

An important issue concerns the diabetogenicity of pregnancy. The higher prevalence of diabetes among women who have borne children and the ability of pregnancy to unmask the latent diabetic have raised the possibility that the recurrent metabolic stresses of pregnancy may be causing or accelerating the appearance of diabetes among women. A related issue concerns the morphologic changes that occur in the pancreas of the infant of the diabetic mother. This finding combined with the higher frequency of diabetes among children of diabetics raises the possibility that the maternal environment, in the presence or absence of a genetic predisposition, may be playing an etiologic role in the development of diabetes mellitus. Many intriguing studies support these

concepts, but considerable investigation is needed before hard answers become available.

B. PREVALENCE OF DIABETES IN PREGNANCY

1. OVERT DIABETES

The frequency of overt diabetes mellitus in the obstetrical population is commonly considered 1/200 to 1/1,000 (1, 2, 3). The higher of these figures is found in a city hospital where the specific estimate was found to be 0.51 percent ±0.23 (2). The difficulty in estimating an accurate national figure can be inferred from a survey of all 27 hospitals in the Cleveland area, where diabetes was revealed to occur once in every 359 pregnancies (3). However, this figure varied from 1 to 196 in one hospital to 1 in 2,500 in another (3). Thus, the prevalence rate on this basis will vary according to local interest, diagnostic habits and standards, as well as with local referral practices. This problem will not be resolved in such a way as to allow extrapolation to the U.S. population until both the numerator and denominator can become amendable to more accurate definition.

An alternative assessment of the magnitude of the total problem can be obtained by estimating the size of the eligible population. This is available through the 1973 Health Interview Survey data, which show 443,000 women in their childbearing years reporting diabetes mellitus (4).

It may be noted parenthetically that prevalence rates fail to reflect the many young women with diabetes who never appear in the obstetrical population because of discouragement attributable to their own fears and/or advice against pregnancy by health personnel.

2. GESTATIONAL DIABETES

As an early form of diabetes, making a transient appearance in pregnancy, gestational diabetes must be considered separately. An accurate prevalence rate for this stage of the disease would require that every member in the enumerated, unselected population have a diagnostic glucose tolerance test. One city hospital obstetric population surveyed for this asymptomatic condition had a rate of 2.3% with a standard error of 0.5% (5). This rate can be considered reliable because both a well-defined numerator and denominator were obtained, but it has the limitation of representing a single geographic area and of being confined to a low socioeconomic group. Nevertheless, it clearly indicates that gestational diabetes occurs at least four to five times more frequently than overt diabetes.

3. CONCLUSION

Diabetes associated with pregnancy occurs in up to 28 cases per 1,000 pregnancies, with the early transient asymptomatic stage of the disease -- gestational diabetes -- appearing more frequently than overt, previously diagnosed diabetes, at a ratio of 4 or 5 to 1. More data are needed to verify these figures and to examine socioeconomic and racial influences on the rates.

4. FUTURE DIRECTIONS

a. GOALS

The purpose of future studies is to establish acceptable prevalence rates for both overt and gestational diabetes according to the strict standards of the epidemiologic method.

b. APPROACHES

A variety of geographic areas can be selected, with a combined representativeness that will allow extrapolation of the findings to the whole U.S. population. It must be possible to enumerate the total prenatal population in each area in a specified time interval. Casefinding must assure the application of the diagnostic test (GTT) to all patients, or, if a predefined diagnostic algorithm is employed, then a random sample of each population should have the diagnostic test without prerequisites. The characteristics of nonparticipants should be explored to exclude major biases. Detailed attention to laboratory quality control and accuracy, with "blind" interstudy exchanges of blood samples, should be an integral part of such studies.

C. DIAGNOSTIC TESTS AND STANDARDS

1. INTRODUCTION

Overt symptomatic diabetes can be diagnosed simply by demonstrating and confirming hyperglycemia. The early asymptomatic appearance of diabetes, on the other hand, requires a standardized tolerance test and a common set of criteria for diagnosis.

Falling into this category of asymptomatic diabetes, gestational diabetes is generally defined to be glucose intolerance confined to pregnancy in a person who was previously not known to be diabetic. Over 95% of these persons, selected prospectively, revert to normal postpartum,

while a remaining few percent remain diabetic (1). Gestational diabetes is a common condition affecting an estimated 1% to 2.5% of the pregnant population, depending on the criteria used (5-8).

It has been repeatedly shown that gestational diabetes is associated with increased fetal mortality, which generally is at least double that of the overall mortality rate in any hospital (7, 8, 9, 10). Reported failure to confirm this mortality may be due to imprecise criteria for selecting gestational diabetics (11). Since up to eight gestational diabetic patients are seen for every overt diabetic in pregnancy (12), fetal mortality due to gestational diabetes becomes more common than that due to overt diabetes in pregnancy. Now, there is evidence that this mortality can be reduced with insulin management (13, 14).

Finally, identification of gestational diabetes is an important clue that the mother will develop overt diabetes later on (6).

Despite the abundance of evidence that gestational diabetes is common and treatable, it is not being searched for effectively or consistently in American pregant women. Several reasons must be considered. One is that the available evidence is not generally appreciated by the practicing physician. A second reason is that there is a lack of agreement on which patients to test for possible gestational diabetes, which test to use, and how to interpret test results. Another is that the success of insulin treatment in reducing perinatal mortality needs confirmation. This section of the report focuses on the second problem: selecting a test and setting criteria for its interpretation.

To test for gestational diabetes, glucose may be administered either orally or intravenously and the levels of glucose in the blood observed. The consensus for use of these tests in nonpregnant subjects is that the oral glucose tolerance test (oral GTT) is more sensitive and less reproducible, the intravenous glucose tolerance test (IV GTT) is less sensitive and more reproducible (15). Whether or not this generalization applies to pregnancy is a matter of debate.

2. ORAL AND INTRAVENOUS GLUCOSE TOLERANCE TESTS IN PREGNANCY

After a woman is selected for glucose tolerance testing through screening, then a choice of a test must be made. An extensive experience is available with the oral glucose tolerance test in pregnancy, beginning in 1942 when Hurwitz and Jenson first observed an increased frequency of glucose intolerance in late gestation (16). The Diabetes Field Research Unit study of gestational diabetes in Boston, covering a period of 17 years, is the most important subsequent body of experience with the oral test. This study has provided the only population based criteria for the diagnosis of diabetes in pregnancy using any glucose tolerance test (17).

Another publication from this group established that mild carbohydrate intolerance occurs normally in the third trimester (7). This finding has been confirmed (18) and is consistent with the insulin resistance (19) and enhanced maternal fat breakdown characteristic of late gestation in both human and animal models of pregnancy (20, 21).

One early criticism of the oral test was that gastric emptying is slower in late gestation and that the glucose absorbed by the body would be delayed over a longer period of time (22). While gastric emptying is delayed in late gestation, the criteria of O'Sullivan and Mahan (17) are specific to early third trimester so that alterations in rate of absorption are irrelevant (Table 1). However, at the time (1950's and 1960's), criteria for the glucose tolerance test in the nonpregnant state were being used in pregnancy. Thus, there was some justification for a test of carbohydrate tolerance that circumvented the pregnancy effect of glucose absorption by the intestine.

Attention was turned to the intravenous glucose tolerance test (IV GTT). The effectiveness of the intravenous test can be evaluated in at least two ways. First, the test must be consistent with other things we know about pregnancy, especially the insulin resistance and impairment of oral glucose tolerance in the third trimester (mentioned above). Secondly, the test must be able to detect the gestational diabetic at least as efficiently as the oral test. Each of these questions will be examined in turn.

3. PHYSIOLOGICAL CHANGES IN PREGNANCY REFLECTED IN THE IV GTT

The first study of the IV GTT in pregnancy was performed by Johnson and Bonsnes in 20 pregnant women who were anywhere from the fourth to the tenth month of gestation (Table 2). Eleven nonpregnant women served as controls (23). While the glucose results were not analyzed in terms of exponential rate of decay, qualitatively the IV GTT in late gestation was a little different than control. For example, the difference between the glucose means in pregnancy at 5 and 60 minutes was 156 mg/100 ml and in the nonpregnant women was 153 mg/100 ml. Between 15 and 30 minutes, the differences were: pregnant, 41 mg/100 ml; and nonpregnant, 40 mg/100 ml. It is possible that the failure to find an impairment of glucose tolerance was due to the fact that the subjects were distributed from the second through the third trimester when, as we will see, glucose tolerance may be improved. In 1954, Burt performed IV GTT's in three separate groups of 20 subjects each: nonpregnant, pregnant (a mixture of second and third trimester), and four to five days postpartum (22). Again, no statistically significant difference in glucose tolerance could be obtained. The accuracy of the glucose determinations in these early studies can be approximated by whether a third trimester reduction in the fasting glucose was detected. As shown in Table 2, at least the trend is seen in every report.

TABLE 1

CRITERIA FOR THE ORAL (100GM.) GTT IN PREGNANCY

Gestational diabetes is diagnosed, in the absence of overt symptomatic diabetes, when two or more of the following blood glucose values* are met or exceeded:

Fasting	–	90 mg per 100 ml.
One Hour	–	165 mg per 100 ml.
Two Hour	–	145 mg per 100 ml.
Three Hour	–	125 mg per 100 ml.

*Values are given for venous whole blood autoanalyzer (Hoffman), or equivalent, add 14% for plasma or serum values.

Table 2

TABLE 2

IVGTT IN NORMAL PREGNANCY

Authors	Glucose* Analysis	Glucose Dose (g)	Sampling Times (min)	Fasting Lower Third Trimester	Subjects	k (%/min)	Interpretation
1. Johnson and Bonsnes (23)	Folin-Wu Benedict	25	0, 5, 15, 30, 60, 120	Slightly (82 vs 77 mg/100 ml)	Potential diabetics excluded (evenly distributed from 4th - 9th mo)	-	No significant difference
2. Burt (22)	SN	25	0, 15, 30, 60	Yes	Unselected		No significant difference (trend is toward a slight deterioration)
3. Silverstone, Solomons, and Rubricus (24)	SN	25	Every 10 min for 60 min.	Borderline lower	Potential diabetics excluded	NP 1.67+0.08† 1TM 2.42+0.14 2TM 1.92+0.09 3TM 1.91+0.10 PP 1.58+0.08	The difference between NP and 3TM is not significant
4. Bleicher, O'Sullivan, and Freinkel (27)	SN	25	Every 10 min for 60 min.	Yes	Potential diabetics excluded	3TM 1.41+0.09‖ PP 1.29+0.12	
5. Billis and Rastogi (28)	AA	25	Every 8 min for 72 min.	-	Normal and diabetic suspects	2TM 1.95+0.33 § 3TM 1.61+0.50 3TM 1.45 3TM 1.46 3TM 1.15 PP 1.50	
6. Picard, Ooms, Balasse, and Conard (25)	AA	23/70 Kg (0.33g/Kg)	Every 5 min for 45 min.	-	Potential diabetics excluded	NP 2.9 Early P 3.1 Late P 1.5	
7. O'Sullivan, Snyder, Sporer, Dandrow, Charles (26)	AA	25	Every 10 min for 60 min plus a sample at 5 min.	Yes	Intentionally random selection (every 10th registrant)	30wks 2.02+0.05** 11wks 2.53+0.10 PP	

* All analyses were on whole blood unless otherwise indicated. SN=Somogyi Nelson Method. AA=Autoanalyzer Method
† Mean values or slightly lower in two later publications on the same numbers of subjects (30, 31). Results are means $\pm$ SEM.
‖ Mean $\pm$ SEM
§ Mean $\pm$ SD
** Calculation of k was individualized to be based on that portion of the curve between 5 and 60 minutes that is linear after log transformation.

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In 1961, Silverstone, Solomons, and Rubricus (24) performed IV GTT's in separate groups of 20-30 subjects, who were nonpregnant, pregnant (in the first, second, or third trimesters of pregnancy), or a few days postpartum. They calculated the expotential rate of glucose disappearance by plotting absolute glucose values on semilog paper and calculating the k rate as $k = \frac{69.3\ t}{2}$. The results showed a progressive decline in k over the three trimesters. The third trimester values were significantly greater than postpartum, and the second and third trimester values together were greater than those of the nonpregnant group. However, a significant difference was not seen in the most important comparison, nonpregnant versus third trimester pregnant. It is well to remember that all of these subjects were preselected to have none of the factors that suggest gestational diabetes. Thus, if a more representative population group had been studied, the mean values (particularly in the third trimester) could well have been lower (more about this below) relative to Picard et al. (25) and O'Sullivan (26). The important point from this study is that a sequential change is seen over the three trimesters consistent with the progressive contrainsulin effect characteristic of normal pregnancy. It is of interest that a trend toward a lower fasting glucose seen in the third trimester in these data was not significant.

Bleicher, O'Sullivan, and Freinkel did paired IV GTT's in the third trimester and six days or more postpartum in ten subjects (27). These subjects were also selected (as in the case of Silverstone et al.) to be completely without any history suggestive of diabetes. A slightly higher k value was seen in the third trimester, but the difference was not significant.

A declining trend in intravenous glucose tolerance during the course of gestation was recorded by Billis and Rastogi (28), who did paired glucose tolerance tests in the second and third trimester in 21 subjects who were a mixture of normal and diabetic suspects. Again, a decline in k rate was observed in the third trimester. Sixteen women suspected of having diabetes were given paired tests in the third trimester and postpartum. Here, also, a lower k rate occurred in the third trimester. In this study, a group of 50 subjects screened to be without suspicion of potential diabetes had a third trimester k rate of 1.73 ±0.31 (SD), which compares favorably with Silverstone (24). A smaller group of normal subjects (9) tested before the third trimester had a higher k rate of 2.51 ±0.56 (SD), further confirming Silverstone et al. (24).

The downward trend in IV glucose tolerance in gestation is again reported by Picard, Ooms, Ballasse, and Conard (26). Separate groups of nine subjects each were in the nonpregnant state, in early gestation or in late gestation. In this report, the k value was highest in early gestation, lowest in late gestation, and intermediate in the nonpregnant

group. In earlier work, the authors found no difference between non-pregnant and third trimester k values (26). Nonetheless, a declining trend within the confines of gestation is seen in both reported series. A higher k value postpartum (in one of the author's reports) may be due in part to a lower dose of glucose (given on a per Kg basis) (Table 2) and a shorter sampling time (45 minutes). A shorter sampling time will tend to eliminate the effect of a more rapid glucose return to baseline and a flattening of the curve in the postpartum GTT (see discussion of O'Sullivan's work, below).

The question of the IV GTT has more recently been examined by O'Sullivan, Snyder, Sporer, Dandrow, and Charles (26), who performed paired tests in 149 subjects in the third trimester and six or more weeks postpartum. Every tenth registrant at a prenatal clinic was tested, which means that all subjects, whether normal or potentially abnormal, entered into the study. A significant reduction in k in late gestation (Table 2) was found to be significant at the <0.005 level. These data are not necessarily as incompatible with earlier reports as might first appear.

Most other studies purposely excluded subjects who might have had undetected diabetes. It is the gestational diabetic who would be expected to most strongly skew the data towards a lower level in the third trimester, although only two or three would be expected in a group of 149. On the other hand, the disparity between O'Sullivan and previous authors may be ascribed to how the k rate is determined. Previous authors, with the exception of Picard et al. (25), have taken the 10-60 minute log transformed data, and constructed a straight line visually or by the least squares method, regardless of any remaining curvilinearity.

The important finding of O'Sullivan et al. is that the log transformation does not uniformly correct for curvilinearity (26). In addition, there is a more rapid return to a fasting level (and a nonlinear portion of the curve) postpartum than antepartum. These authors corrected for this effect by picking in a reproducible fashion the linear portion of the curve for the calculation of k. This maneuver would have the effect of selectively raising the postpartum k value higher than the antepartum value. Apart from the possible effect of a few gestational diabetics, this manipulation could itself reveal a difference between pre- and post-partum where it had been previously obscured. Indeed the postpartum value reported by O'Sullivan et al. (26) is higher than all reported values (24, 27, 28), with the exception of Picard et al. (25) (Table 2). As noted above, these authors sampled only through 45 minutes in the IV GTT and may have fortuitously avoided the postpartum effect or an earlier glucose return to baseline that would artificially lower the k rate. More recently, O'Sullivan and coauthors have analyzed the effect of a 37.5 vs. 25 mg dose of intravenous glucose (29). A higher dose increased the k rate. Assessment of k rates as "glucose excess" over

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post-test **leveling** eliminated the effect of body weight. However, the effectiveness of a higher dose in detecting diabetes was not determined.

Confirmation of a reduction in intravenous glucose tolerance in late gestation must be left to further careful study of some of the problems mentioned above. Whatever the final conclusion, the available data are consistent on a very important point, that intravenous glucose tolerance decreases as gestation proceeds (24, 25, 28). This trend is consistent with the view that a biphasic shift occurs in pregnancy towards enhanced anabolism in early gestation and enhanced catabolism with increased insulin resistance in late gestation (20, 21). This consistency is an independent kind of proof that the IV GTT can detect a diabetogenic state and therefore can be of value in looking for the gestational diabetic.

4. SETTING A NORMAL STANDARD FOR THE IV GTT

The inclusion or exclusion of potential diabetics is not a small issue when attempting to set standards for diagnosis. As there is no all-or-none basis for diagnosing mild diabetes -- for instance, as it occurs in pregnancy -- arbitrary statistical norms must be relied upon. From the epidemiological point of view, these norms are best based upon a representative population sample which includes a few cases of the disorder one wishes to detect in the proportion that they usually occur in that population. Then, given a representative sampling, norms can be constructed to detect the top 10%, 5%, 2.5%, or 1% of the group. The eventual success of any of the discriminant levels can be tested eventually, but at the outset their use is arbitrary. To exclude subjects with the potential disorder from the initial population base is to make finding a diagnostic level even more arbitrary and pragmatic.

In the case of the IV GTT, standards have not yet been set from the only population based study available (26). In the other studies of Silverstone et al. (24) and Billis and Rastogi (28), norms have been picked for each of the three trimesters but are based on subjects preselected to be normal, are based on small numbers, and are based on populations about which nothing is known. In the third trimester, Silverstone's lower limit (2.5% confidence interval) for k is 1.13 and has seen the most general use. Interestingly, Billis and Rastogi obtained a lower limit of 1.17, 2 SD below the mean of their log transformed data (28). As a preliminary test of his own data, O'Sullivan has used the Silverstone cutoff of 1.13 as a level for assigning the diagnosis of diabetes in gestation (7). The number of pregnancies detected with perinatal mortality resembled the experience with the oral glucose tolerance test. Thus, at the moment a k cutoff of 1.13 appears to be a serviceable lower limit of normal until larger studies of the question are performed. The fact that the linear glucose decline is greater in antepartum than postpartum (26) may explain the substantial

degree of agreement among studies for the k rates during the third tri-
mester despite the inability to agree on a value postpartum.

5. CASEFINDING EFFICIENCY OF IV AND ORAL GLUCOSE TOLERANCE TESTS

Differing conclusions have been drawn about which test, IV or oral,
is "best" for diagnosing mild diabetes in pregnancy. It is the thesis
of this review that the varied interpretations are due primarily to dif-
fering and often arbitrary definitions of normal and abnormal. Less
frequently, the amounts of glucose administered and the physiological
differences in the tests themselves may bear on which test is "better."

The details of these papers are reviewed on Table 3. In general,
all of the studies were performed with 25g glucose intravenously and
200g orally. Glucose analyses were done by "true glucose" methods:
Somogyi Nelson or Autoanalyzer techniques which are known to give
comparable results. All determinations were done on whole blood rather
than on plasma. Efforts at dietary preparation varied, but as a normal
2000 calorie diet ordinarily contains 200g carbohydrate, it is unlikely
that these differences were meaningful.

The greatest differences among the studies consist in the criteria
for interpreting the oral test and in the selection of pregnant subjects
for study, the subjects being all normal, all suspected diabetics, or a
mixture of the two. Criteria selection for the intravenous tests
appears to have been less of a problem since most papers use the criteria
of Silverstone et al. (24) or closely approximate them.

The earliest studies can be grouped together because they all used
oral test criteria that were not specific to pregnancy. In the case of
Welch (30), the Public Health Service Criteria were used; in the cases
of Kaplan (31), Hagan (32), Ocampo et al. (33), and Benjamin and Casper
(34, 35), criteria approximating those of Fajans and Conn were used.
With the hindsight provided by the criteria specific to early third tri-
mester pregnancy of O'Sullivan and Mahan (17), it is clear that both
PHS and Fajans and Conn criteria are inappropriately applied to pregnancy.
Specifically, both of these criteria specify upper limits of normal of
two and three hours of 120 and 110 mg/100 mil respectively as opposed
to the pregnancy criteria at two and three hours of 145 and 125 mg/100 nal
respectively. These seemingly small differences in glucose produce large
differences in patient selection, and larger numbers of abnormal subjects
where the lower test levels are employed.

In Welch's study of 27 pregnant subjects abnormal by the oral (PHS)
test criteria, 30% were abnormal by the IV test criteria (30). At
delivery, there was only one overweight infant in the IV normal group,
while there were three perinatal deaths and two overweight infants in
the IV abnormal group. The conclusion of this study was that the IV test

TABLE 3

COMPARISONS OF IV AND ORAL GLUCOSE TOLERANCE TESTS IN PREGNANCY

Authors	Glucose Analysis*	Dosage (g) IV	Dosage (g) Oral	Dietary Preparation	Criteria IV	Criteria Oral	Subject Selection	Abnormal Tests(%) (N)	Abnormal Tests(%) IV	Abnormal Tests(%) Oral
1. Welch (30)	SN and AA	25	100	>250g for 3 days	<3%/min†	PHS || (any 2 or more values)	Diabetes suspects	(27)	30	100
2. Kaplan (31)	SN and AA	25	100	>300g for 3 days	Fixed levels at 68 and 120 min §	1 <161, 2 <110	Mixture of normal and diabetes suspects	(8)	0	100
3. Solomons, Silverstone and Posner (36)	SN	25	100	2000 cal diet	<1.13	-	OB Hx: Glycosuria: OB + Fam Hx:	(18) (25) (7)	33 4 21	- - -
4. Ocampo, Coserlu, and Quilligan (33)	AA	25	100	300g for 3 days	<1.13**	0 <110, 1 <160, 1 1/2 <140, 2 <120, 3 <110 (any 2 or more values)	Potential diabetic excluded	(22)	0	55
5. Billis and Rastogi (28)	AA	25	50	250–300g for 3 days	<1.40††	Peak <150, 2 <100	Group A: Normals, Group B: Potential diabetics	(50) (101)	8 46	8 16
6. Benjamin and Casper (34)	AA	25	100	None	<1.13	0 <110, 1 <160, 2 <120	Diabetes Suspects	(200)	32.5	70.0
7. Benjamin and Casper (35)	AA	25	100	None	<1.13	Same	Diabetes Suspects	(144)	4.3	10.6
8. O'Sullivan (26)	AA	25	100	>150 for 3 days	<1.34	0 < 90, 1 <165, 2 <145, 3 <125	Random Selection	(% fetal losses in diabetics) 8.0%		9.5%

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TABLE 3

COMPARISONS OF IV AND ORAL GLUCOSE TOLERANCE TESTS IN PREGNANCY (CONT'D)

Authors	Glucose Analysis**	Dosage IV (g)	Oral	Dietary Preparation	Criteria IV	Oral	Subject Selection	Abnormal Tests(%) IV	Oral
								(% perinatal abnormalities)	
9. Hadden, Hartley, Kajtar, and Montgomery (38)	AA	25	50	250-300g for 3 days	<1.40	1 <140 2 <110	Diabetes suspects A: Normal Suspects B:	8.1 7.2	10.8 6.2
10. Silverstone, Posner, Pomerance, and Cramer (39)	SN	25	100	2000 Cal. diet	1 TM <1.37 2 TM <1.18 3 TM <1.13	0 < 90 1 <165 2 <145 3 <125	Mostly Diabetes Suspects	12.1	6.7

* All analyses were done on whole blood unless otherwise indicated; SM = Somogyl - Nelson method, AA = autoanalyzer method.

† Method of Amatuzio where "glucose excess" above fasting is plotted semilogarithmically. Unless otherwise stated, glucoses are measured every 10 min for 60 min.

‖ PHS criteria are: 0 Hr: <110, 1 Hr: <170, 2 Hr: <120, 3 Hr: <110. Unless otherwise stated, glucoses are measured at 0, 1, 2, and 3 hours.

§ IV test was abnormal if the 68 min glucose value exceeded 26 mg% above fasting and was above 100 mg% at 2 hours.

** Blood drawn at 0, 10, 25, 40, and 55 min.

†† Blood drawn at 8 min intervals for 72 min.

‖‖ Antepartum tests compared to subjects who had a positive cortisone CTT postpartum. 47% of these subjects had a normal IV test antepartum while only 12% had an abnormal oral test.

correctly identified more pregnancies at risk than the oral test, the oral test yielding more false positives. These conclusions are consistent with the view that oral test criteria are inappropriate and overdiagnose diabetes in pregnancy. It should be noted the IV test criterion used by Welch is based on nonpregnant criteria and the Amatuzio method of assessment. This criterion is probably appropriate, since we have already seen that a reduction in third trimester IV glucose tolerance is very difficult to show (22, 23, 24, 27, 26).

In 1961, Kaplan studied eight pregnant subjects with IV and oral glucose tolerance tests and a tolbutamide tolerance test as well (31). All eight subjects had abnormal oral glucose and tolbutamide tolerance tests, but none had abnormal IV tests. In this study, the oral test may be overdiagnosing diabetes, but also the IV test could be underdiagnosing since (for instance) the blood glucose is almost certainly below 100 mg/100 ml after two hours unless the subject has fasting hyperglycemia. A similar experience was reported by Hagan in 1961 with 46% abnormal oral tests and 0% of abnormal IV tests (32). Likewise, Ocampo et al. found 55% of 22 subjects abnormal by the oral test and none abnormal by the IV test (33). The IV test in this series appropriately selects no one since potential diabetics were excluded on the basis of history. In the series of Benjamin and Casper (34), only diabetes suspects were tested. Nonetheless, the same excess of positive oral tests is seen relative to the IV test, with 32.5% positive by the oral test. Interestingly, when Solomons et al. screened diabetes suspects with the IV test, they identified almost the same number of persons, particularly where obstetrical history was used (36).

Benjamin and Casper performed a follow-up study (35), using the cortisone primed oral glucose tolerance test done postpartum as a reference point. The same excess in antepartum oral tests is apparent whether the postpartum test was negative (10.6% positive oral vs. 4.3% positive IV) or positive (47% positive oral vs. 12% positive IV).

A different rate of diabetic casefinding in pregnancy was reported by Billis and Rostogi in 1966 (28). In normal subjects the rates were about the same; in diabetic subjects, the IV test identified three times as many persons as the oral (Table 3). In the Belfast study, 50g oral glucose were administered as is customary in Great Britain (37). Anything above a blood glucose of 150 at the peak time and above 100 at two hours was considered abnormal in the oral test (Mosenthal and Barry criteria), and a k value below 1.40 (1 SD or more below the mean) was considered abnormal in the IV test. While it is difficult to judge the stringency of the oral criteria in pregnancy because of the lower glucose dose, it is clear that the IV criteria would select as abnormal one-third (1 SD) of a normal population and an even larger number of the group pre-selected as diabetic suspects. These expectations are borne out in the results.

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TABLE 5

Trends of Course of Pregnancy by Class

Class	Spontaneous Abortion Rate	Hydramnios Degree	Excessive Weight Gain	Preeclampsia	Large Placenta	Heavy Birth Weight	Fetal Loss			Congenital Anomalies	Diabetes Intensification
							Introuterine	Intrapartum	Neonatal		
A	N	+	+	+	++++	++++	+	++++	+	+	+
B	N	++++	++++	++++	++++	++++	++	++++	+	+	++++
C	N	+++	+++	+++	+++	+++	+	++	++	+	+++
D	+	++	++	++	++	++	+++	+	+++	+	+
E	++++	++	++	++	+	+	++++	+	++++	+	+
F	++++	±	0	?	0	0	++++	+	++++	+	±
R	++++	±	0	Super-imposed?	0	0	++++	+	++++	+	±

from White, P.

In the series of Hadden et al. in 1971, the number of fetal abnormalities seen with abnormal tests is the reference point (Table 3). The incidence of perinatal abnormalities was rather low. There were not significant differences between oral and IV tests. Since criteria for both tests were low (for instance, the k value of <1.40 is at 1 SD below the mean), perhaps any selectivity in the tests is diluted out by the presence of many "falsely negative" individuals (38).

The most recent study of Silverstone, Posner, Pomerance, and Cramer (39) illustrates the excellent concordance between oral and IV tests when proper criteria are applied. The concordance was particularly high in the negative tests. Twice as many subjects were positive by the IV as against the oral test. It is interesting to speculate that the fewer abnormal oral tests may be due to the fact that the O'Sullivan test criteria were applied to an earlier time in gestation where standards for oral test interpretation do not exist. At a time earlier than the third trimester, it may well be that the upper limits for glucose are lower at the second and third hours of the oral test. Nonetheless, the concordance between IV and oral in this study is much better than earlier. In 1970, when O'Sullivan reported his experience with the IV and oral tests (7), rather than comparing the concordance in casefinding, he reported perinatal losses in subjects abnormal by the oral and IV tests. In the IV tests, the lower tenth percentile ($k \leq 1.34$) yielded 8.0% viable losses as compared to 1.9% in the group $k > 1.34$. This difference is not significant because of the small numbers involved. When 107 subjects with both oral and IV tests abnormal were tested, no significant differences in viable losses were shown between the two groups. Use of a lower cutoff of 5% (Silverstone's $k = 1.13$) did not change the interpretation of the results obtained with a cutoff of $k = 1.34$. The concordance between IV and oral tests in this analysis can probably be attributed to the use of appropriate criteria in both tests.

6. SUBSTANTIATION OF THE CRITERIA

The previous section indicated both problems with, and the relations between, the diagnostic tests in current use. An alternative assessment can be accomplished by observing women with gestational diabetes in the years following the pregnancy that unmasked the condition. The only extensive study of this kind concerned patients at Boston City and Boston lying-in hospitals. The actual observed rate for varying intervals of follow-up to sixteen years was 43%, while the application of life table techniques to compensate for the unequal intervals yielded an estimated 60%. In selected control patients with negative glucose tolerance tests, on the other hand, only 2% (3.8% by life table) were subsequently found with diabetes. Diabetes in the follow-up studies was diagnosed by the comparatively strict U.S. PHS criteria based on a recommendation by an expert advisory committee to the U.S. Public Health Service (40). The substantiation of the criteria for gestation diabetes, and indeed of

the U.S. PHS criteria, became a truly in-depth one when a further 12-year extension of the observation interval demonstrated the health status of these individuals, in terms of carbohydrate control, years following the diagnosis of diabetes as well as documenting their development of cardio-vascular disease (42, 43). The conclusion from the Boston studies gives considerable credence to the criteria for the oral glucose tolerance used to diagnose gestation diabetes in that they enabled the researchers to select women, with a high degree of accuracy, years before the disease became overt.

7. <u>CONCLUSIONS</u>

This review attempts to show that the casefinding ability of the IV and oral tests is a function primarily of the criteria used. Physiologically, both tests probably reflect the increasing insulin resistance of pregnancy, although the oral test may reflect more hepatic glucose assimilation and the IV test more pheripheral.

Also gut factors and islet responsiveness should play a greater role in the oral test. In fact, considering the important physiological distinctions between the oral and the IV test, it is surprising that the concordance in casefinding (39), in detecting perinatal abnormalities (38), and in predicting risk for perinatal death is as good as it is. Since the pathophysiology of gestational diabetes (or any kind of diabetes) is not yet clear, it is impossible to prefer one or the other test on physiologic grounds. The earlier criticism of delayed gastric emptying in pregnancy affecting the interpretation of the oral test can now be dispensed with as pregnancy-specific criteria are now in use.

In terms of diagnostic criteria, deficiencies still exist for both IV and oral tests. In the IV test, trimester-specific criteria have been available since 1963 (36), but these are based on small groups of people (no more than 30) from whom any suspected diabetics were excluded. Thus these criteria need to be confirmed in a larger and randomly selected population that includes the number of abnormal persons that ordinarily occur in a population. With respect to oral criteria, the possibility has not been assessed that different criteria may be needed in the first and second trimesters when anabolic shifts are more important than catabolic in the metabolism of glucose by the mother (20, 21). It is also possible that socioeconomic distinctions may exist. The oral test criteria were obtained in a large city hospital setting (17). It is possible that different criteria might be applied to a more affluent private practice setting. This consideration could apply to the IV test as well.

Just as a clear distinction cannot be made between the casefinding selectivity of oral and IV test using present criteria, so also no distinction can be made in terms of practicalities of performing and interpreting the test. Advantages of the IV test include its brief duration

(one hour) and the avoidance of nausea and vomiting that may affect 5% or 10% of women taking the oral test. The reduction of the IV test into a simple k value is an advantage. However, how to calculate the IV test is not entirely agreed upon, and the subtleties of calculation may make widespread clinical use difficult. In this respect, interpreting the oral test is much easier. Certainly the oral test can be administered by a technician. Formerly, the IV test required a physician to inject the glucose, but the trend now is to delegate these tasks to qualified nurses.

If one were forced to choose now between the IV and oral tests, the oral test should probably be selected simply because it is better standardized, is better understood by more people, and has been used more often by both investigators and clinicians. An additional reason is that it is the only test that has been adequately substantiated through documentation of overt diabetes in the years following pregnancy.

Further research will be required to determine if there is any other basis for preferring one test over the other.

8. FUTURE DIRECTIONS

a. GOALS

The purposes of future studies will be to refine existing diagnostic criteria and the related methodology; to expand to include standards for each of the trimesters of pregnancy; to explore socioeconomic and racial influences; to explore and validate alternative screening techniques documenting the influence of time of day, laboratory methodology, and the desirable frequency of testing; and to validate diagnostic criteria for gestational diabetes through periodic observation of these patients in subsequent years.

b. SPECIFIC OBJECTIVES

1) Establish criteria for the full oral GTT specific to the first and second trimesters. Confirm the existing criteria for the third trimester in other socioeconomic groups.

2) Establish guidelines for retesting diabetes suspects who tested normal at an earlier time in gestation.

3) Oral and IV test criteria should be derived for both whole blood and plasma glucose to avoid the necessity of using arbitrary conversion factors from one to the other.

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4) Determine if the three-day period of high carbohydrate feeding is necessary prior to testing, and establish recommendations if high carbohydrate feeding is necessary.

5) Explore the role of the size of the glucose challenge used in the intravenous and oral tests in pregnancy, in particular, the potential of larger-than-usual doses for discriminating between diabetics and normal patients.

6) Support studies for looking at attendant measurements of hormones and other metabolites to determine if the specificity of the GTT can be improved in the future when these measurements become more physically and economically accessible to the practicing physician and the general public.

7) Study new or preferably existing populations of gestational diabetics for overt diabetes in their subsequent years. This critical and ultimate test of the validity of criteria must be employed for patients diagnosed by either the oral or intravenous glucose tolerance test, or by both.

D. SCREENING FOR DIABETES IN PREGNANCY

1. STATE OF THE ART

Because full glucose tolerance testing is time consuming and expensive, certain indications are relied upon to justify glucose tolerance testing. These indications are directly associated with our knowledge of early diabetes. The concept that diabetes could be identified years before it became clinically apparent arose from the observation of the unusual obstetric histories given by diabetic women. As a direct result, the transient appearance of diabetes in pregnancy has been, and continues to be, sought among women reporting the birth of babies weighing over nine pounds or having congenital malformations, those reporting toxemia or other complications of pregnancy, those with stillborn babies or babies who died in the neonatal period, and those with a family history of diabetes. In addition, women exhibiting glycosuria are frequently the target of screening programs (37, 44, 45) despite the low threshold for glucose that occurs with pregnancy. It has been demonstrated that use of casual glucosuria alone for detecting is poor, with over 50% of patients exhibiting positive tests in pregnancy (46, 47); consequently, this test does little more than provide a rationalization that a detection program is in operation.

There is no doubt that the yield of gestational diabetics can be increased by requiring several of the screening factors to be present in

each patient, but only at the expense of leaving undiagnosed a greater number of the total available gestational diabetic women. Similarily, a subset of glucosuric patients found to have glucosuria on a second fasting were found to show a greater yield of abnormal intravenous glucose tolerance tests than those who were negative to this repeat testing procedure (44). However, the data are indadequate for calculating sensitivity and specificity rates for fasting glycosuria. Data meeting this quality requirement are available, however, for screening blood glucose levels obtained one hour following the ingestion of 50 grams of glucose, and they result in a sensitivity of 79% and specificity of 87% (5). This approach, used without regard for the clinical history, minimizes the number of both false negatives and false positives.

Despite the adéquacy of post glucose screening, it has not been widely adopted primarily because it is demanding and more costly, because the available evidence is unappreciated, because clinical history screening programs are already in operation, and because, in centers with good antenatal care, the perinatal loss rates have been reduced to accepted levels. The surprisingly poor showing of the clinical history phenomena, in the very patients that gave great impetus to research into the "prediabetic" phase of the natural evolution of diabetes mellitus, might have been anticipated. For example, the number of women with a history of bearing large babies in the general population is numerically far greater than the few associated with diabetes, despite the fact that the proportion of women with a large baby history is five times greater among diabetic women, and diabetes itself exists in only 2% to 3% of the population.

The falling perinatal loss rates do not obviate the necessity for an adequate screening program. In the first place, all patients do not have good antenatal care. Secondly, early detection in pregnancy, at least in the experimental model, may emerge as an integral part of reducing the risks of diabetes in the offspring, as will be discussed later. Finally, screening the current pregnancy is important in terms of identifying for early prenatal care patients who may have progressed to a more overt stage of diabetes prior to a subsequent pregnancy.

2. CONCLUSION

In the variety of methods employed in screening prenatal patients for diabetes, most are inefficient. The only fully documented method indicates a glucose measurement one hour after 50 grams of oral glucose to be the most effective procedure. Alternative methods need evaluation, including the exploration of the effects of time of day and duration of pregnancy. Clinical experience indicates that effective screening for diabetes in pregnancy is widely neglected despite its established worth.

3. FUTURE DIRECTIONS

    a. GOALS

        1) Explore and simplify methods of screening for gestational diabetics.

        2) Develop educational programs for physicians seeing obstetrical patients to present the state of the art as it is and promote screening for gestational diabetes.

    b. APPROACHES

        A variety of screening methods should be applied to a prenatal population, including a variety of post glucose and postprandial intervals -- using whole blood and plasma glucose; modified history phenomena (e.g., birth weight at ten pounds or greater; closer degrees of relationship for family history, etc., than previously used); and glucosuria under differing circumstances. These methods can be evaluated by the glucose tolerance test, but an essential component in the design will be to apply the GTT to an adequate, random sample without regard to the presence of positive screening factors.

E. MATERNAL MORTALITY

1. STATE OF THE ART

The introduction of insulin dramatically altered the high toll in maternal deaths associated with diabetes and pregnancy. By 1959, maternal mortality in diabetic patients had declined to 0.03-0.07% compared with the 0.032-0.037% for the general population (48). Subsequent reviews indicate that maternal mortality is essentially equivalent to that in the normal population, though documentation is lacking. Dr. Priscilla White reports three known maternal deaths attributed to myocardial infarction in the first trimester (49), which suggests an increased risk that needs to be identified for diabetic women at various ages, preferably by the White classification.

The records of the Massachusetts Maternal Welfare Committee showed 2,420,930 live births between 1954 and 1973. There were 787 maternal deaths (.03%), with 16 diabetes related. Using the full range of estimates for diabetes in pregnancy, these figures imply a 4- to 22-fold increase in maternal mortality; using the cited average figure of 1 in 359 pregnancies, they imply an 8-fold increase. More recent statistics, for 1969 to 1974, show 113 maternal deaths, of which three were diabetes

related, indicating that the proportion of the total maternal diabetes related deaths has risen from 2.03 to 2.35%. Undoubtedly, more refined (and continued) data recording and analyses are needed, but these reports do suggest the possibility of an eight-fold excessive maternal mortality for women with diabetes.

2. CONCLUSION

The evidence of a higher maternal mortality among pregnant diabetics needs urgent confirmation. The role of specific causes must be assessed.

3. FUTURE DIRECTIONS

A specific study of maternal deaths should be undertaken. Problems with methods used for documenting diabetes as a contributory or under-lying cause have been dealt with elsewhere (Scope Workgroup on Mortality). It is essential to review all maternal deaths to determine if diabetes was present or excluded, regardless of the stated cause of death, in order to assess the scope of the problem. To establish effective pre-ventive programs, researchers will need detailed analyses of specific causes. The results of a specific study should indicate the appropriate recommended changes in current methods of recording mortality infor-mation for maternal deaths.

F. MATERNAL MORBIDITY

1. VASCULAR COMPLICATIONS

Vascular complications, which may be graded by the widely adopted White classification, play an important role in assessing the risks of pregnancy in the diabetic. Historically, calcification of pelvic blood vessels on X-ray was noted to be associated with a poor prognosis for the pregnancy, and from this finding the White classification was developed for identifying the overt or probable degree of vascular disease present (see Table 4). Of the 870 patients seen at the Joslin Clinic between 1958 and 1970 who reached 28 weeks of pregnancy or more, the distribution was as follows:

Class	Number of Cases	Percent
A	32	4
B	181	21
C	212	24
D	340	39
E	4	less than 1
F	79	9
R	22	3

In a more recent Joslin series of 448 patients seen between 1965 and 1975 with 813 pregnancies, the distribution by class was follows: A-3%, B-21%, C-28%, D-30%, F-8%, R-6% and F-R-4%. In class D, vascular disease is clinically detectable in the form of retinopathy in about 85% of these patients. Pedersen's Copenhagen series from 1959-1963 showed a similar distribution except for a larger percentage of Class A's (50). Dolger's series of 253 patients in New York from 1952 to 1962 showed a predominance of Class A's and B's (51). Clearly, the reported frequencies will depend on local referral patterns and the zeal with which Class A diabetics are sought. The classification indicates that a high proportion of overt juvenile diabetics have vascular disease in pregnancy. Pregnancy, however, does not appear to affect the development of the vascular disorders. White found no difference in the frequency or severity of vascular disease between nullipara and multipara (1), and Hagbard came to a similar conclusion in a follow-up study of 514 diabetic mothers (52).

Clinically detectable coronary artery disease in pregnancy has a very poor maternal prognosis and is considered a strong contraindication to pregnancy. Interruption of pregnancy is generally urgently advised, although Dr. Priscilla White has reported one successful pregnancy in a diabetic woman six months after saphenous bypass surgery for coronary artery disease that was manifested by angina (49).

Peripheral vascular disease has not been a major complication of pregnancy. In general, this occurs in patients with macrovascular disease, usually a late manifestation of juvenile diabetes. Only one patient in Dr. White's experience of 22,000 patients required a toe amputation for gangrene during pregnancy.

2. DIABETIC RETINOPATHY AND PREGNANCY

a. INTRODUCTION

In general, the study of diabetic retinopathy has had little clear scientific documentation. The recent attempts being made in the National Diabetic Retinopathy Study may bring scientific validity to the observations on diabetic retinopathy. In the

TABLE 4

WHITE CLASSIFICATION OF MATERNAL DIABETES

Class A: G.T.T. abnormal. No symptoms. Euglycemia maintained without treatment except appropriate diet.

Class B: Adult onset (age 20 or older) or short duration (less than 10 years).

Class C: Relatively young onset (age 10-19) or relatively long duration (10-19 years).

Class D: Very young onset (age less than 10) or very long duration (20 years or more), or evidence of vascular disease (i.e., retinopathy).

Class E: Pelvic vascular disease (by X-ray).

Class F: Renal disease.

Class R: Retinitis proliferans or vitreous hemorrhage.

past, reports on the relation between pregnancy and diabetic retinopathy have been contradictory: pregnancy is said to induce rapid progression, have no effect on diabetic retinopathy, have a beneficial effect on diabetic retinopathy with remissions occurring following the completion of pregnancy, etc. In a group of juvenile-onset diabetic girls who developed diabetes under the age of 15, whose duration of diabetes was greater than 15 years, and whose pregnancy occurred in their twenties, Dr. Aiello reports that a brief review of his photographic files shows the following contradictory events during pregnancy:

Case 1: Young patient had proliferating retinopathy which went into spontaneous remission before pregnancy, and no exacerbation occurred during an ensuing pregnancy or in five years of follow-up.

Case 2: Had proliferating diabetic retinopathy start within the first trimester, progress rapidly during the second trimester, and end in vitreous hemorrhage upon delivery of the baby, not clearing except through vitrectomy surgery some six to eight months after term.

Case 3: Proliferating diabetic retinopathy developed at the beginning of the second trimester in both eyes. Photocoagulation, using pan-retinal Ruby laser technique, resulted in remission in the treated eye. However, remission also occurred in the untreated eye, both eyes being 20/20 six months following delivery and both eyes having remained clear of any retinopathy for more than five years and through two further pregnancies.

No studies since Waite and Beetham (1932) have given us clear-cut information with regard to the natural course of diabetic retinopathy, let alone, the natural course of diabetic retinopathy in pregnancy.

b. PREVALENCE OF DIABETIC RETINOPATHY IN PREGNANCY

Retinopathy appears in the minority of diabetic women during pregnancy, occurring in 20% between the ages of 20 and 29, 22% between the ages of 30 and 39, and in only 4% in patients between the ages of 10 and 19 (53). It has been estimated that the range of retinopathy observed in pregnancies is from 25% (54) to 41% (55).

c.   RISK TO VISION

    Small series (55-58) suggest that patients with nonprolif-
erating diabetic retinopathy do not tend to get worse during
pregnancy. White suggests that nonproliferating diabetic reti-
nopathy waxes and wanes during pregnancy without tendency to
progress (1, 54, 60).   Beetham (55), Janert (58), and White
(1, 59) suggest that proliferating diabetic retinopathy has a
greater but unpredictable tendency to progress during pregnancy,
especially if the proliferating phase is noted during the first
trimester.

    In White's series, the proliferating retinopathy in ten of
144 obstetric patients was advancing rapidly at the time of
pregnancy. Preretinal and vitreous hemorrhage developed in
this small group as early as the first trimester. Blindness
occurred in 11 of the 20 eyes. In three patients, both eyes
were involved. Of the 144 patients, no progression was noted
in 70%. The appearance of cotton wool exudate and flame hemor-
rhages was typical in the 30% showing progression, with these
changes most commonly noted in the third trimester. Vision
was not seriously impaired in relation to the pregnancy in 93%
of the 144 patients (these 144 obstetric patients all had pro-
liferating diabetic retinopathy; the average duration of
diabetes was 17 years with onset less than 15 years of age in
91%).

    It would be difficult to state that the progression described
here represents an increased rate compared to the natural
course of proliferating diabetic retinopathy without pregnancy,
as the latter also can exhibit a very rapidly progressively
downhill course over a few months' time. Further, it seems
"rather certain" that a considerable portion of patients whose
retinopathy progresses during pregnancy will show regression
after delivery (57, 58, 59, 61, 62). A carefully controlled
study following diabetics of the same age -- with and without
pregnancy and with and without retinopathy -- is necessary to
evaluate fully the risk to vision.

d.   RETINOPATHY RELATED TO OUTCOME OF PREGNANCY

    Fetal loss rate is said to increase with the increasing
severity of retinopathy, which severity is apparently correlated
with the presence of angiopathy elsewhere, especially in the
kidney. These differences seem to be much more striking in
studies reported by Dr. White in 1956, in which fetal survival
was over 80% when no diabetic retinopathy was present, about
60% when nonproliferating diabetic retinopathy was present,

only 20% when no proliferating retinopathy was noted. However,
in the later series reported by White in 1971, the percentage of
live-born and surviving infants whose mothers had proliferating
diabetic retinopathy only was 42%, nephropathy only was 52%,
and combined proliferating diabetic retinopathy and nephropathy
35%. The viable salvage rate for the series as a whole was 64%:
74% for infants whose mothers had proliferating retinopathy alone,
65% for those whose mothers had nephropathy alone, and 54% for
those whose mothers had combined lesions. The frequency of
severe congenital abnormalities was 13%. Clearly the fetal
survival in the presence of retinopathy has improved since the
1956 reporting by White, et al.

e. MICROANGIOPATHY

Ditzel reported exaggerated venous dilatation, and develop-
ment of microthrombi intensified in the bulbar conjunctiva of
White's group of 144 patients with proliferating retinopathy.
Subsequent studies by Ditzel have expanded his studies of
microangiopathy into a general hypothesis to explain the develop-
ment of retinal, renal, and other lesions based on tissue oxygen
availability/demand ratio with injury due to recurring tissue
hypoxic episodes (79, 81). His concept is an intriguing one,
and particularly attractive in its potential for preventive
medicine by the employment of simple phosphate treatment (81).
Although hypothesis is in an early state of development, con-
trolled trials are now a possibility.

f. SUBSEQUENT COURSE OF MOTHERS AND OFFSPRING

The death rates of the mother from renal failure were not
changed by pregnancy. Eventual renal failure leading to fatal
uremia occurred in 16 of 144 women (12%), expectation of life
period after a rise of BUN to 25 mgm. was not changed (6 years).
Eventual blindness after pregnancy occurred in 12 patients (+6
already blind), or 12%. The average age of death was 35; the
duration of diabetes, 23 years; the time interval since pregnancy,
eight years until death. Of 32 who died of this series, 28
deaths were related to the diabetes. Of the children, two
developed diabetes: one, chemical diabetes at age four; and one,
overt diabetes at age ten. Gigantism occurred in four. Three
children died in infancy: one from an accidental scalding, one
from congenital heart disease, and one from muscular dystrophy.

g. SUMMARY

The frequency of diabetic retinopathy in pregnancy, while
uncertain, is cited as between 25% and 41%. Nonproliferating

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retinopathy does not appear to worsen during pregnancy. **Prolif-erating** retinopathy has a tendency to progress with serious impairment of vision in 7%, but it is unpredictable and it is not known whether this experience is different from the natural (and also unpredictable) progression in the nonpregnant diabetic. Perinatal mortality is higher in diabetics with retinopathy than in those without, despite the improvement described in more recent studies. Life expectancy for the mother, already compro-mised by the presence of proliferating retinopathy, did not appear to be altered. Blindness subsequent to pregnancy was noted in 12% of one study of 144 mothers with proliferating retinopathy.

3. NEPHROPATHY

The prognosis·for renal function is good in those whose renal insufficiency is mild enough to sustain pregnancy without resort to renal dialysis (63). A retrospective analysis of fatal diabetic nephropathy, however, shows that, even without pregnancy -- once the mean creatinine reaches 3 ± 1 and mean BUN 40 ± 10 -- the average prognosis for life apart from transplant and dialysis is only about three to four years (64). There is no firm evidence that pregnancy will either improve or aggra-vate the prognosis for the mother (65, 67). Indeed, it is likely that pregnancies in women with this level of retinopathy will terminate spontaneously in abortion. The unpredictable variability of angiopathy -- particularly with retinopathy, which is discussed in a separate section -- requires that objective evidence from a controlled setting is needed before any conclusion in this regard can be reached.

4. POSTPARTUM HYPOPITUITARISM

Severe midline or diffuse headache with nausea and vomiting that lasts three or four days has occasionally been associated with postpartum hypopituitarism.

5. INFECTIONS

Infections during pregnancy are more of a problem when the patient has diabetes. Otherwise self-limited gastroenteritis can be a special hazard to the insulin dependent diabetic and seems to create even more problems in the management of the pregnant diabetic, where the metabolic state of accelerated starvation enhances susceptibility to ketoacidosis. The poor tolerance of the diabetic for this metabolic insult is associated with up to 50% fetal mortality. Urinary infections are seen commonly in the form of asymptomatic bacteriuria, not infrequently as symptomatic cystitis, and occasionally as severe pyelomethritis. Frank Veglsgaard

demonstrated asymptomatic bacteriuria to be four to five times as frequent in diabetic as in the nondiabetic pregnancies (68). Instrumentation of the urinary tract must be asiduously avoided to eliminate a potential source of infection. In 1969, Ponetta, Rees, Younger, and Kass reported the study of 253 pregnant women with diabetes screened during prenatal visits, with results suggesting that the combination of angiopathy and bacteriuria are particularly lethal to the fetus (69). Pedersen also recognized pyelitis as one of his four major Prognostically Bad Signs during Pregnancy in the diabetic, the others being toxemia, ketoacidosis, and neglectors.

6. MATERNAL COMPLICATIONS OF PREGNANCY

Maternal complications are presented schematically in Table 5.

a. TOXEMIA AND ECLAMPSIA

Toxemia and eclampsia have been reported in diabetic pregnancies, with frequencies varying from 8-70% (48, 71). Some 7-10% are normally quoted in the nondiabetic (72, 73). The variation in the diabetic rates probably reflects a difference in diagnosis, in the category of diabetes seen, and in the timing of delivery.

b. HYDRAMNIOS

Hydramnios in diabetics is reported in from 3-100% (74, 75), while generally occurring in 1% of nondiabetics. The diagnosis, a subjective one, varies enormously according to the observer.

c. PLACENTA

In a comparative study of its structure by Bernstein et al. (76), the placenta exhibited arterial endothelial thickening with deposition of mucopolysaccharide and luminal narrowing. The magnitude of the changes appeared to correlate with fetal loss. Microscopic studies of the maternal vessels at the implantation site (decidual) show acute atherosis and hyalinization in many diabetic patients (77, 78).

7. CONCLUSION

Maternal morbidity is increased for the pregnant diabetic, with enhanced risks for the pregnancy. The vascular complications of diabetes play a prominent role here, since their presence and severity appear to correlate with the size of the perinatal mortality rate. On the other hand, the evidence for any permanent effect of pregnancy on the complications of diabetes is weak, arising primarily in connection with proliferating retinopathy. The unpredictable variability in the course of vasculopathy underscores the need for much greater study of this aspect.

8. FUTURE DIRECTIONS

   a. GOALS

      Studies of greater quality are needed but pose formidable
   problems. The presence of vascular disease is difficult to
   measure, particularly in its early stages. Advances in non-
   invasive techniques of evaluation and the improved quality of
   retinal vascular assessment will facilitate future studies of
   the effects of pregnancy on maternal morbidity. Understanding
   diabetic retinopathy in pregnancy, in which measurable changes
   can occur over a short period of time, might help our under-
   standing of its etiology and pathogenesis, and also enhance the
   possibility of identifying the factors associated with the
   unpredictable deterioration of vision characteristic of the
   disease.

      Follow-up studies designed to reveal any permanent effect
   of pregnancy on the maternal prognosis for vision, renal failure,
   and cardiovascular disease are required.

   b. APPROACHES

      A collaborative, multicenter cohort study of pregnant dia-
   betics with retinopathy and similarly afflicted nonpregnant
   females and males as controls should be instituted. Serial stero-
   photography, retinal vascular flow with fluorescein and newer
   laser techniques, hemobarometry for a greater understanding
   of the hemodynamics, rheology with particular reference to red
   cell clumping -- these procedures, in addition to complete
   visual and ocular examinations by qualified ophthomologists,
   should all be considered for the cohort study protocol. The
   Diabetic Retinopathy Study of the National Eye Institute could
   be used as a model for the investigation. Similar cohort studies
   of the renal and cardiovascular complications seen in the
   pregnancy of the diabetic are needed. There are no alternatives
   to cohort studies for revealing the natural history and the
   influence related variables such as, in this instance, the con-
   trol of diabetes, changes in metabolic interrelations, or micro-
   angiopathy and cellular hypoxic injuries (79, 80, 81).

                  G. OVERT DIABETES AND THE OUTCOME OF PREGNANCY

1. STATE OF THE ART

The destructive relation between diabetes and pregnancy was particu-
larly evident in the pre-insulin era. Williams reported on 82 pregnancies

in 1909 from which 25 women died and 53 babies failed to survive (82). With the introduction of insulin and the employment of a multidisciplinary approach to the pregnant diabetic, a dramatic improvement in the prognosis for the pregnancy has occurred. However, maternal diabetes continues to be one of the most common causes of problems to the fetus and the newborn child.

The introduction of the White classification for diabetes in pregnancy greatly facilitated communication between centers as well as providing a prognostic index. Table 6 presents the perinatal deaths for the Joslin Clinic 1940-1956 series (83). The White classification of graded severity from A through F is found to correlate well with the perinatal mortality rate as shown on the table.

A series particularly revealing of the problem is illustrated by the recent prognostic review by Dr. White of a total of 156 pregnancies in 81 women whose diabetes was diagnosed before the age of six (Table 7-12). These patients were seen between 1934 and 1974. There were 112 live babies. Nineteen pregnancies were interrupted because of renal failure. Seventeen aborted spontaneously. Twenty-five had neonatal or intrauterine deaths. There were 25 perinatal losses, or 28% perinatal mortality. Four of the 81 patients were classified as "diabetic dwarfs," two of whom had successful pregnancies and two of whom did not. Duration of diabetes was very long. Only seven had diabetes less than 15 years. Seventy-eight had diabetes for 15 to 25 years, 11 for 25 to 29 years, and 4 for 30 to 35 years. When the duration was 10 to 15 years, the survival was 88%; 15 to 19 years, 80%; 20 to 25 years, 72%; and 25 to 35 years, 62%.

This relatively uniform group of long-term patients thus again confirms the prognosis for pregnancy as related to duration of diabetes. The age of the mother was also relevant. In 24 cases where maternal age was 30 to 35 years, the fetal salvage was only 42%. When the mother was 20 to 30 years old, 83% were successful; and for those 15 to 20 years of age, 88% were successful. This is consistent with recommendations that young women with diabetes plan to complete their families early. Fifty-one percent had retinopathy. In 35%, it was background retinopathy, and in 16%, retinitis proliferans.

Three patients were actually blind. Two blind patients had successful pregnancies, one delivering surviving twins. One of these patients had an amputation for peripheral vascular disease prior to pregnancy. Nine percent had diabetic nephropathy. The maternal survival was 57 (70%), known to be alive in 1974. Seventeen (21%) were dead and seven (9%) were untraced. The deaths included two with carcinoma of the breast, one with liomyoma of the stomach, and one with melanoma of the thigh. The cause of death in these young patients was primarily cardiorenal disease.

Table 6

PERINATAL DEATHS-RELATION TO
SEVERITY OF MATERNAL DIABETES

No.	Class	
11	A	0%
202	B	13%
279	C	16%
209	D	27%
35	E	29%
31	F	39%
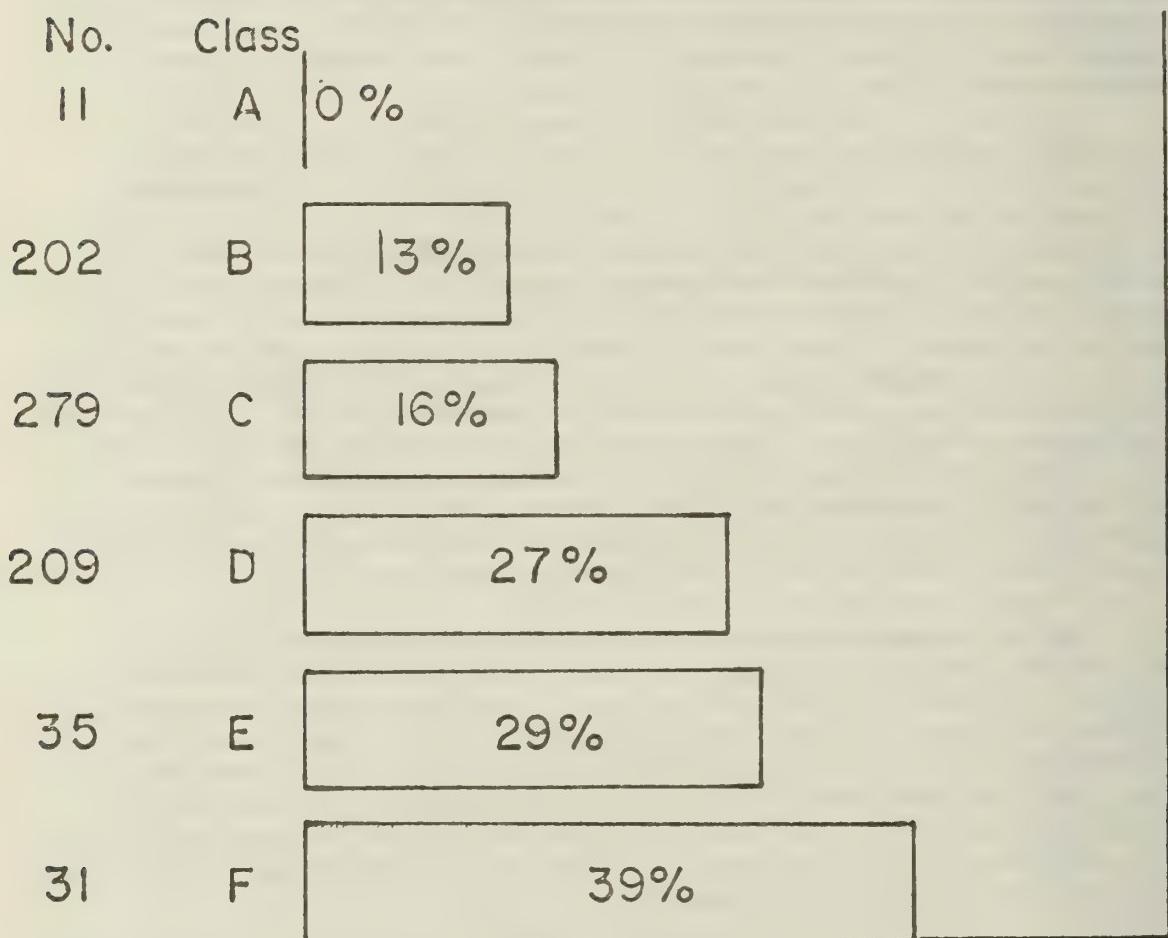
Data from Joslin Clinic 1940-1956 Gellis, S.S. & Hsia, D.Y.: AMA J. Dis. Child. 97:1, 1959.

TABLE 7

PREGNANCIES IN PATIENTS WITH DIABETES ONSET UNDER AGE 6

JANUARY 1934 - JANUARY 1974

81 Patients (Onset Under Age 6)

156 Pregnancies

158 Infants

Interrupt............2.................1%

Failures........... 44 .... 28%
    (19 Previable)

Success...........112.................71%

Viable Success...................... 82%

TABLE 8

D_1 – Onset $<$ 10.................. 156

D_2 – Duration $>$ 20............... 99

D_3 – Benign Ret.................. 35

D_4 – Cal. Art. Legs

D_5 – Hypertension

E – Cal. Pel. Arter............... 8

F – Nephropathy.................. 13

R – Ret. Prolif.................. 16

Cardiopathy

TABLE 9

VASCULAR LESIONS

Retinopathy 51
    Benign. 35
    Malignant. 16

Blind 3

Calcified Arteries 23%

Hypertension 9%

Nephropathy. 9%

Amputation. 1

TABLE 10

DURATION D.M. AT TIME OF PREGNANCY

%

< 15 yrs............................7

15–25 yrs........................... 78

25–29 yrs.......................... 11

30–35 yrs.......................... 4

Shortest............ 13 yrs

Longest.............33 yrs

TABLE 11

FETAL SURVIVAL ACCORDING TO DURATION D. M.

Duration	Survival
10 – 14.9 yrs.	88%
15 – 19 yrs.	80%
20 – 24.9 yrs.	72%
25 – 35 yrs.	62%

TABLE 12

FETAL SURVIVAL AS TO AGE OF MOTHER

Age	Survival
30 – 35	42
20 – 29.9	83
14 – 19.9	88

Maximum number of pregnancies = 5

A current series (1958-1970), Table 13, illustrates the extent of the improvement in the more recent past, and Table 14 shows the rate of perinatal survival through the years. Reports are now appearing which reflect yet further advances taking place in specialized centers (83a, 84). For example, Kings College Hospital reports that no losses were experienced with the employment of bed rest in the later stages of pregnancy, careful blood sugar control, and the employment of careful testing of the feto-placental integrity and fetal maturity assessments to guide the critical timing of delivery (84). These latest advances are still undergoing evaluation and their results are being observed with optimistic caution because runs of excellent results have been noted in the past.

The graded relationship between the White classification and perinatal mortality poses an important investigative challenge. It has not been possible to isolate the factor(s) related to the increase in fetal wastage in the diabetic mother. Maternal age, duration of diabetes, and vascular disease are closely intertwined in the classification. More data are required in order to reveal the relative roles that can be assigned to each of these components and to such factors as the control of hyperglycemia throughout gestation. The current improvements in perinatal mortality will make a valid study of contributing variables more difficult to achieve except through large cooperative trials. In addition, authorities in the field emphasize the need to use additional evaluative endpoints (85). The concern being expressed relates to the quality of the offspring and whether the abnormal maternal environment is facilitating the development of congenital malformations or neurologic deficits that may handicap the future lives of these children (86, 87).

a.   THE PREVALENCE OF CONGENITAL MALFORMATIONS

The occurrence of congenital malformations in infants of diabetic mothers has always been of great concern. Since the beginning of the insulin era when diabetic females were able to carry a pregnancy to term, physicians have sensed that there was a greater occurrence of congenital malformations in infants of diabetic mothers than in the general population (1).

However, in order to be assured of this view, large series of diabetic pregnancies had to be observed by one team and compared to the known general occurrence of congenital malformations in the population. In addition, the population samples had to be comparable in origin and size.

A few centers were in the position of realizing this, because of the centralizing of the care for diabetics in a rather stable population where the in-and-out migration was minimal. The largest series available is in East Germany (88). Then follow the 20-year experience in the Bispebjerg Hospital, Copenhagen (70);

TABLE 13

PERINATAL SURVIVAL ACCORDING TO CLASS

JOSLIN CLINIC SERIES

JUNE 1, 1958 to JANUARY 1, 1970

Class	No. of Patients	Perinatal survival (%)
A	32	94*
B	181	92
C	212	92
D	340	89
E	4	100
F	79	79
R	22	86
TOTALS	870	90

*One Rh negative patient delivered 2 intrauterine deaths with fetal hydrops.

TABLE 14

PERINATAL SURVIVAL IN

JOSLIN CLINIC VIABLE PREGNANCY* SERIES

1922 THROUGH 1973

	No.	Infant Survival %
1922-2 to 1938-1	128	54
1938-1 to 1958-6**	900	86
1958-6 to 1974-1**	1118	90
	2146	

* 28 weeks of gestation and beyond

**Treatment included Estrogen and Progesterone given parenterally.

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the experience of the Pediatric Department, Child Life and
Health Center in Edinburgh (89); and the Joslin Clinic
experience. The observation of these centers with 360 to
2,000 diabetic pregnancies seen by one team over 20 years
confirms what had been sensed in smaller previous series.

It should be noted also that the severity of the congen-
ital malformations has to be defined in order to achieve
comparable figures. If fatal congenital malformations are
accounted for with death during the first ten days of life,
the different series reach a minimum figure for the prevalence
of congenital malformations, a figure three times higher in
infants of. diabetic mothers (6-8%) than in infants in the
general population (1-2%) (70, 88, 89, 90).

The occurrence of congenital malformations in autopsy mate-
rial also confirms its greater frequency among infants of dia-
betic mothers. If one takes the definitions of "major," "fatal,"
and "multiple" malformations the percentages are four, six, and
six times higher, respectively, in diabetics than the general
population (90).

In a diabetic-prone population the frequency of congenital
anomalies among the infants was shown to be relatively high in
nondiabetic persons but significantly higher in diabetic patients
(1.9% versus 3.8%). This study indicates again that diabetes
increases by a factor of six the natural in-built tendency
toward congenital malformations (91). Early-onset of diabetes
was especially associated with the particular risk of bearing
anomalous children in this study. The prediabetic period was
not associated with a higher incidence; however, the normal
rate of congenital malformation was already high. A comparison
with other epidemiological investigations in other tribes has
not been made.

Minor congenital malformation can be more difficult to study
accurately, but frequency is greater in infants of diabetic
mothers. The percentages cited by different authors vary widely
(from 10-40%), apparently because of observer variation; this
indicates that clear endpoints such as fatal malformation have
to be taken into consideration in order to have comparable figures.

b. TYPE OF CONGENITAL MALFORMATIONS

Different organs can be involved: the heart, the kidneys,
the central nervous system, the umbilical cord, and the bones.
In some series, Pedersen et al. 1964 (92), Driscoll 1961 (93),
Herre and Horky 1964 (94) showed a predominance of heart and

large vessels malformations and severe limb deformities. In
other series, the malformation of the central nervous system
occurred with greater frequency (Pedersen 1967) (70). Sacral
agenesis occurred in 1 out of 380 diabetic pregnancies, while
it occurred in only 1 in 250,000 in the normal population, and
therefore can be considered characteristic of but not pathogno-
monic for diabetes (Amendt et al., 1974; Kucera et al., 1968).
In situations where variations in the prevalence of a specific
malformation are reported, geographical differences have to be
contemplated (Pedersen).

c. MATERNAL CHARACTERISTICS RELATED TO CONGENITAL MALFORMATIONS

1) In relation to the duration of the disease in diabetic mothers:
   When diabetic women are classified according to White's classi-
   fication, a major increase in the percentage with congenital
   malformations occurs in women with vascular complication of
   the disease (10%). The frequency of congenital malformation
   may therefore be three times higher when vascular compli-
   cations have occurred. There is no difference in the general
   distribution of the organs involved in relation to the com-
   plications of diabetic mothers (70, 88).

2) In relation to the metabolic status of the mother:
   The congenital malformations with fatal outcome occur with
   greater frequency when the blood sugar widely exceeds the
   normal range and especially if the mother developed ketoacidosis
   at the beginning of her pregnancy (83). There is also an
   indication that more minor hypoglycemic episodes occur during
   the first trimester of pregnancy in women who do not have
   infants with congenital malformations. However, other aspects,
   unknown hitherto, have to be taken into account as congenital
   malformations may also occur in infants born to gestational
   diabetics (95, 96).

   In the obstetrical histories of women who later become dia-
betic, infants with congenital malformations can be found (97).
It is also apparent that this is not a single event. Women who
have had an infant with a congenital malformation will also have
a greater frequency of abnormal obstetrical phenomena (repetitive
malformations, stillborn infants, miscarriages, heavy birth-weight
infants) (98). The studies indicate that for any one woman, birth
of an infant with a congenital malformation not not be a unique
feature but another expression of poor reproductive function where
metabolic disturbances facilitate this expression of failure in
reproduction.

   That women with diabetes mellitus in their family may be more
prone to failure in reproduction is apparent from the study of

Downing and Goldberg (1956) (99). The authors found that among 100 children with ventricular septal defect, 31% had a family history of diabetes. Among 100 children with interauricular septal defect, 20% had a diabetic heredity by history only. In a general prenatal population comprising 18,812 patients, the frequency of a family history of diabetes was found to be 9%.

d. EXPERIMENTAL WORK WITH CLINICAL IMPLICATIONS

The role of the metabolic disturbances in diabetes during pregnancy is possibly permissive in nature, as it appears from the experimental observation of Horii et al., 1966 (100). In a strain of mice with a specific bone malformation, the increase of its occurrence was fivefold when the mice were experimentally made diabetic before pregnancy. When the mice were treated with insulin in an optimal fashion bringing the blood sugar back to normal, the percentage of congenital malformations was reduced again to normal for that strain of mice.

e. SUMMARY

Major, fatal, and multiple congenital malformations are increased at least three times in infants of diabetic mothers, with the percentage higher (sevenfold increase) when vascular disease is present. The absolute prevalence in the latter circumstance is about 10%. Lesions may be located in any organ: heart, large vessels, kidneys, central nervous system, bones. They are related to the severity of the disease as expressed by the vascular complications. However, other factors are possibly involved in the diabetic-prone woman which may increase her built-in tendency for reproductive failures. There is a clear indication also that malformations occur in relation to poor diabetes control, particularly ketoacidosis in early pregnancy.

2. CONCLUSION

Despite recent advances in the management of the pregnant diabetic woman, perinatal mortality -- even in highly specialized centers -- remains higher than in the nondiabetic. These mortality rates, based on the White classification of the extent of vascular complications, reach 26% in patients with proliferating retinopathy. Yet the critical factor in the high perinatal mortality is unknown. The relative roles on the outcome of pregnancy of maternal age, duration of diabetes, vascular disease, and diabetes control are not known or understood. Studies must no longer confine their endpoints to perinatal mortality but also include the degree of normality attained by the surviving infant. Congenital malformations of the major, multiple, and fatal variety occur three times

more commonly in the diabetic situation, a finding that is increased in the presence of maternal vascular disease or poor diabetic control, particularly ketoacidosis in early pregnancy. Some encouraging experimental evidence in animals shows that control of diabetes can prevent congenital malformations.

3. FUTURE DIRECTIONS

   a. GOALS

      The effect of diabetes on pregnancy has intrigued diabetologists for its potential in providing a model which will increase our understanding of the mechanisms of diabetic complications in general. Consequently, it becomes imperative to have data which clearly separate relative effects of maternal age, duration of diabetes vascular disease, and metabolic control on perinatal mortality. Existing data should be explored with more sophisticated analytic techniques, and new studies should be implemented. A more specific short-term model exists in the vasculature of the placenta. In the short span of nine months, the growth and development and finally death of this vascular structure take place -- providing an ideal setting for contrasting, by electron-microscopy, nondiabetic matched controls with diabetic persons of various ages and duration of diabetes both with and without clinical vascular complications.

      The studies of congenital malformations should include documenting the extent of their excessive number in circumstances related to diabetes. The type of defect and the possible effects of geographic location must be explored. It is no longer adequate to perform studies retrospectively by record review. Classification differences and observed variation confound existing studies (101). A common protocol and prospective controlled studies requiring each infant to have a standardized examination are essential.

   b. SPECIFIC OBJECTIVES

      1) Encourage the development of centers for the treatment of the pregnant diabetic including the availability of a diabetologist, a perinatologist, and a neonatologist as a specialized team. These centers would then be a resource for prospective and cross-sectional studies of diabetes.

      2) Study the specific effect of maternal age, duration of diabetes, vascular complications, and metabolic control on the outcome of pregnancy.

3) Use a standardized examination, based on an accepted classification of congenital malformations, of both diabetic and control infants to study the recess usually seen with diabetes. Multicenter studies may provide clues of geographic origin, particularly if populations with a high prevalence of diabetes (e.g., Pima Indians) are included.

4) Relate maternal and paternal diabetes control to the presence or absence of congenital malformations in controlled studies.

5) Evaluate the costs in hospital care, institutional care, corrective surgery, and special education of infants of diabetic mothers as compared with the infants of nondiabetic mothers.

H. GESTATIONAL DIABETES AND THE OUTCOME OF PREGNANCY

1. STATE OF THE ART

Pregnancy provides the unique opportunity for detection of diabetes in its early stages. The adverse effect upon the fetus of maternal diabetes, even in its virtually asymptomatic stage, has been recognized for many years. The first clues to the seriousness of the maternal prediabetic state came from retrospective studies. For example, Miller and coworkers reported perinatal losses in 1944 amounting to 19.8% in women during the 20-year period preceding the clinical diagnosis of diabetes (102). In the five years immediately preceding the onset of clinical diabetes, perinatal losses in this group amounted to 35.4%. These findings were not isolated phenomena. The following table illustrates the extremely high perinatal mortality rates observed by a number of authors years before the discovery of clinical diabetes:

Perinatal Mortality Rates Before Discovery of Diabetes

Author	Year	Years	Perinatal Mortality (%)
Allen (103)	1939	10	15.3
Miller et al. (102)	1944	5	35.0
Herzstein & Dolger (104)	1946	5	15.4
Barns & Morgans (105)	1948	5	34.0
Paton (106)	1948	5	21.0
Gilbert & Dunlop (107)	1949	5-10	15.0
Moss & Mullholland (108)	1951	5	16.7
Patterson & Burnstein (109)	1951	5	32.0
Pirart (110)	1954	10	38.8
Caballero & Hurtado (111)	1962	5	38.8
Riviere (112)	1963	5	23.0
Botella-Llusia et al. (113)	1967	10	25.6

The studies of J. P. Hoet (114), Wilkerson and Remein (115), W. P. A. Jackson (116), and Carrington et al. (117) gave great impetus to the study of, and established conclusively, the importance to pregnancy of the very earliest phases of diabetes mellitus; for example, early studies at Temple University Medical Center revealed this connection (117). Previous perinatal losses amounted to 30% in asymptomatic women in whom diabetes was suspected. Detection of an abnormality in carbohydrate tolerance made early enough in the pregnancy to permit alteration in management for 72 mothers resulted in a perinatal mortality of 2.9%, but in the 39 other mothers whose disturbance was unrecognized and untreated during the pregnancy, perinatal mortality was 29.6%.

Though often based on inadequate understanding of the basic problems, these early data touched off an enormous number of investigations. Today, much recognition is given to the problem of pregnancy and diabetes, and other prospective studies have evolved: Billis and Rastogi, 1966 (118); Hadden and Harley, 1967 (119); Drury and Timoney, 1970 (120); and Haworth and Dilling, 1975 (121).

In Boston, the outcome of pregnancy in gestational diabetic patients has been studied in a large controlled prospective clinical trial, in which women with normal glucose tolerance tests selected concurrently were followed as controls (9). Among gestational diabetics, there was a significant increase in perinatal mortality, births of large babies (nine pounds or more), and a trend to more obstetric complications (pre-eclampsia and hydramnios) and maternal deaths as compared with the negative controls (9, 122).

Some studies have failed to show an increase in perinatal mortality among similar patients (119, 121), but the inadequacy of the numbers

studied and failure to include random control patients with a demonstrated normal tolerance to glucose prevent any generalizations from their studies. Other possible confounding factors were subsequently discovered in the Boston study, where the perinatal mortality was found to be age dependent -- with all of the losses occurring in women aged 25 years and older (123). The data do not prove that the younger gestational diabetic is not at risk for perinatal loss, but suggest that in the presence of good prenatal care the diabetes may not be a problem.

An important question arises in relation to the treatment of the gestational diabetic patient. Is insulin treatment necessary in a situation where there are relatively small asymptomatic elevations of the blood glucose level? Insulin treatment has been used by some workers: (Omers, 1960 (124); Pedowitz and Shelvin, 1964 (125); Bruins Slot, 1967 (126); Botella Llusia, 1969 (113); Van der Linden, and Mastboom, 1971 (127)). Most dramatically, Botella-Llusia showed that, if insulin treatment was begun by the sixth week of gestation in a group of prediabetic, latent diabetic, and clinical diabetic persons, perinatal mortality (defined from the 28th week of pregnancy through seven days postpartum) was reduced from 48% in untreated pregnancies by history to 14% in 424 observed pregnancies of the same women. However, in the design of the above studies, each gestational or latent diabetic was considered as her own control; that is, she was treated during her current pregnancy, and her previous pregnancy history in which no treatment was given formed the basis of comparison. The difficulty in interpreting such a design, where each woman's history is used as the control for her current outcome, rests on the recognized but puzzling feature of potential diabetes and of diabetes in general, i.e., the occurrence of entirely normal pregnancies before and after a perinatal death (Connon, 1969) (128). However, no documentation exists to relate these normal events to the gestational blood glucose control in each of the pregnancies.

Therefore, to document conclusively the benefits to be derived from insulin treatment, a prospective study with random allocation to "treatment" versus "no treatment" is absolutely vital in order to remove the confusion existing in the delivery of health care to these patients today. A partial answer to this problem exists, but it needs final validation. The Boston study, referred to above, also included an insulin treatment group in the strict random assignment method required of a therapeutic intervention trial. This study showed that management with insulin and diet effected a significant reduction in the number of large babies born to gestational diabetics (121). It did not show initially an effect on perinatal mortality. However, when their data were reanalyzed restricting the question to patients aged 25 years and over and whose treatment commenced prior to the 32nd week of gestation, then insulin treatment was found to effect a significant reduction in the perinatal mortality rate (129). Although this finding was confirmed by an independent form of analysis from the same study, substantiation through an independent study would be desirable for such an important finding (13).

Thus, we see that gestational diabetes has great importance both in obstetrics and medicine. As shown earlier, the gestational diabetic is at high risk for the development of subsequent diabetes. We now see that she is also a high risk obstetric patient who provides an unusual opportunity for preventive therapy.

2. CONCLUSION

Gestational diabetes is a well-defined entity occuring in 2% to 3% of a prenatal population. Its important relationship to an increased perinatal mortality and the high rate of overt diabetes subsequent to the pregnancy confirms its clinical importance. Strong evidence exists for the beneficial effects of insulin and dietary treatment on fetal salvage, but this needs final confirmation. No studies exist to show that treatment of this transient form of diabetes in pregnancy will retard the later development of overt diabetes in the mother. Most centers are not screening adequately for this condition, thus missing opportunities in preventive medicine and the study of the future diabetic.

3. FUTURE DIRECTIONS

a. GOALS

1) The increased perinatal mortality seen with gestational diabetes requires the institution of active screening programs, since strong evidence exists for the beneficial effects of treatment with insulin and diet in reducing the number of losses. A controlled clinical trial should be undertaken to verify this conclusion.

2) The pregnancy of the gestational diabetic should be subjected to intense scrutiny, in controlled studies, to pursue the unique opportunity of studying patients many years before they may develop overt diabetes. Metabolic interrelations, electronmicroscopic study of the blood vessels in the placenta, and exploration of general hypotheses -- such as Ditzel's hypoxia hypothesis (79, 80, 81) -- must be pursued both for their effects on the current pregnancy and their ability to provide clues to the etiology of diabetes-related phenomena.

3) Cohort studies of gestational diabetics should be instituted or, where they already exist, extended to provide information on the stages of early diabetes that adversely affect the outcome of pregnancy, in addition to revealing the natural history of evolving diabetes.

b. APPROACHES

One important reason we do not have more information on the diabetic pregnancy is that no one center sees enough diabetic pregnancies in a short enough time to answer the questions posed. Consequently, the collaborative multicenter trial would appear to be the only reasonable solution. Ten to 12 centers with 3,000 deliveries at each annually would be capable of providing relatively short-term solutions to questions such as the need for insulin therapy for asymptomatic hyperglycemia in pregnancy. The approach is relatively expensive, approximately $500,000 per year per center, but the cost is offset by their value as demonstration projects for excellence of care, and in terms of the possibility of extrapolating the findings on the need for treating asymptomatic hyperglycemia to the whole U.S. population. In addition to intervention trials, such centers would provide a core activity with resources to examine the metabolic and structural derangements associated with gestational diabetes. Cohort studies of gestational diabetics are difficult to perform and relatively expensive in relation to the apparently slow production of new information. For this reason, existing resources should be exploited. Studies with an adequate statistical base, such as the Boston study with its 17 years' follow-up of gestational diabetics, should be encouraged to extend the study by providing skilled manpower and inducements to patients. The alternative investment of time and money to achieve this level of follow-up de novo would seem unacceptable unless a uniquely stable study population is identified.

I. DIABETOGENIC EFFECTS OF PREGNANCY

1. INTRODUCTION

The suggestion that the recurrent metabolic stresses of pregnancy are related to the high prevalence of diabetes in women, as seen in epidemiologic studies, has been dealt with earlier in the section on Epidemiology (Parity and Diabetes).

The possible role of the diabetic's pregnancy in the development of diabetes in her offspring must also be considered. The gross hypertrophy of the islets of Langerhans in the fetus of the diabetic that comes to autopsy suggests the possibility of permanent damage, perhaps caused by overwork and exhaustion of the islets, as in Young's hypothesis of meta-diabetes induced by growth hormone.

2. CLINICAL EVIDENCE

If the diabetic's pregnancy is causally related to diabetes in the offspring, then the children of diabetic mothers should include more diabetics than the children of diabetic fathers. This has, in fact, been claimed (130), but not confirmed by other workers.

White found more diabetic children among the progeny of diabetic women (8% of their children) than among the progeny of diabetic men (2% of their children) (131). Furthermore, in the nondiabetic children of diabetic mothers, she found an accelerated height, weight, and bone development, and abnormal vascular patterns, especially in the bulbar conjunctive. She stated that the children of diabetic fathers did not show the abnormalities of growth of the vascular lesions. These important findings imply a diabetogenic effect attributable to the earlier intrauterine environment. However, they have not been confirmed elsewhere (134).

3. EXPERIMENTAL EVIDENCE

Okamoto has studied the effect of induced diabetes in rats on their offspring over many generations (133). In the first set of experiments, diabetes was produced in adult rats by means of intraperitoneal alloxan. These rats were mated with diabetic and nondiabetic animals and the islets of their offspring examined after the offspring were killed on the 90th day. The number of beta cells was decreased in all of the offspring when the diabetes in the father rat had been present more than 27 days before mating, or in the mother rat more than 24 days. When both parents were diabetic, the decrease in beta cells in their offspring was approximately double that seen when only one parent was affected. Similar results were obtained with rabbits and guinea pigs. An exciting additional finding was that the effect on the beta cells of offsprings of alloxan-diabetic fathers was abolished if they had been treated with insulin and rendered aglycosuric for at least seven days before mating.

In a second set of experiments, diabetes was found to develop spontaneously in the fourth and fifth generation after serial induction of diabetes with alloxan. Among Okamoto's conclusions (133) from these and additional studies are that both male and female sex cells are influenced by the abnormal environment especially on the first and fourteenth day of the last 23 days of spermatogenesis and the last 24 days of oogenesis. These influences on the sex cells on two different dates are additively responsible for the growth disturbance of the beta cells in the islets of Langerhans; even when diabetes has persisted for a long time, if sperm cells or ova are exposed to a nondiabetic environment for at least the last four days of their formation, the diabetes does not affect the islets of the offspring.

These fascinating experiments have profound implications if they apply to the human subject. They would invalidate much work on the genetics of diabetes and provide the basis for a program in the prevention of diabetes.

4. CONCLUSION

It remains inconclusive whether a maternal diabetic intrauterine environment has any lasting effect on the offspring. The experimental evidence suggests that diabetes in either parent may lead to damage of the pancreatic islets of the offspring, a possibly nongenetic effect on the germ cell.

J. SUMMARY REPORT

An estimated one-half million American women in their child-bearing years have diabetes mellitus. A further one million women in the same age group are eligible to develop transient diabetes during pregnancy. Both stages of the disease are associated with an increased perinatal mortality rate. Even with good prenatal care, this rate is five times higher than that for the nondiabetic, and it is two to three times greater still where care is inadequate. Maternal mortality is estimated to be eight times higher for the diabetic mother than for nondiabetic mothers in the United States.

Maternal and neonatal morbidity are also considerably higher in the diabetic population. They also have higher rates for medical and obstetric complications as well as greater hazards to the newborn. The high frequency of major and fatal congenital malformations (at least three times that found in the offspring of nondiabetics) and more frequent postnatal abnormalities such as neurologic and conceptual deficits in the infant of the diabetic mother pose major problems, economic as well as medical. Correctional surgery, special education, and institutional care are of obvious concern, as is the child's increased risk of developing diabetes.

The study of diabetes in pregnancy provides unusual opportunities for all phases of medicine -- preventive, clinical, and research. Education, screening, and a multidisciplinary approach to treatment can effect a major reduction in the high risk factors that threaten the babies of diabetic mothers. Study of the placenta -- a highly vascular tissue that grows, matures, and dies in the short span of nine months -- offers a readily accessible model for studying the effects of diabetes on the vascular system. Exciting animal studies are now challenging the genetic hypothesis by suggesting the possibility that either maternal environment in pregnancy or the metabolic control in either parent prior

to mating may influence the development of the germ cells and predispose the infant to later diabetes -- and that controlling the diabetes could prevent the adverse effects. These studies, in addition to the suggestive relationship between diabetes control in early pregnancy and the appearance of congenital malformations, suggest that greater attention must be paid to the initial stages of pregnancy -- a time when patients are infrequently seen, particularly among lower socioeconomic groups. Finally, pregnancy has the ability to unmask diabetes years before it becomes overt clinically. The possibility of identifying the future diabetic during a "normal" or "incubation" period, therefore, provides a unique challenge not only for research but also for detailed study of the natural history of the evolution of diabetes mellitus.

Recommendations include immediate research to expand our knowledge of effective methods for screening in the different stages of pregnancy. There must also be investigations aimed at resolving conflicts in various diagnostic tests and the criteria used to evaluate them. Mechanisms for the acquisition of data on maternal mortality among diabetics should be instituted, as well as studies to clarify the relative roles of maternal age, duration of diabetes, and cardio-renal-vascular disease on perinatal mortality rates. The effect of pregnancy on the natural history of retinopathy and possible threats to the mother's vision should be clarified. Standards for metabolic control during pregnancy and the effectiveness of various regimens for achieving this control and assessing its effectiveness need considerable study. Evaluation of emerging techniques for fetal maturity assessment in the diabetic mother is essential to the critical timing of their delivery dates. Professional and public education programs are needed to impress the magnitude of the problem on diabetic and potentially diabetic women -- patients who all too often neglect early prenatal care. (See Figures 1-3.)

The development of specialized centers should be encouraged, since few physicians now see a sufficient number of pregnant diabetics to become familar with the intricacies of the problem. Such centers could be the resource for collaborative studies and multicenter trials, essential to the solution of many unresolved problems outlined by this Workgroup. It is important that existing long-term studies of the natural history of diabetes be selectively nurtured to expand our understanding of the dimensions of the problem of diabetes mellitus as rapidly and effectively as possible. Although basic research studies must continue to be emphasized and expanded, they must not, as they have in the past, be at the expense of applied and epidemiologic research.

FIGURE 1

EFFECT OF TREATMENT OF GESTATIONAL
DIABETES ON OUTCOME OF PREGNANCY

SOURCE: (FROM O'SULLIVAN, et al 1971)

232
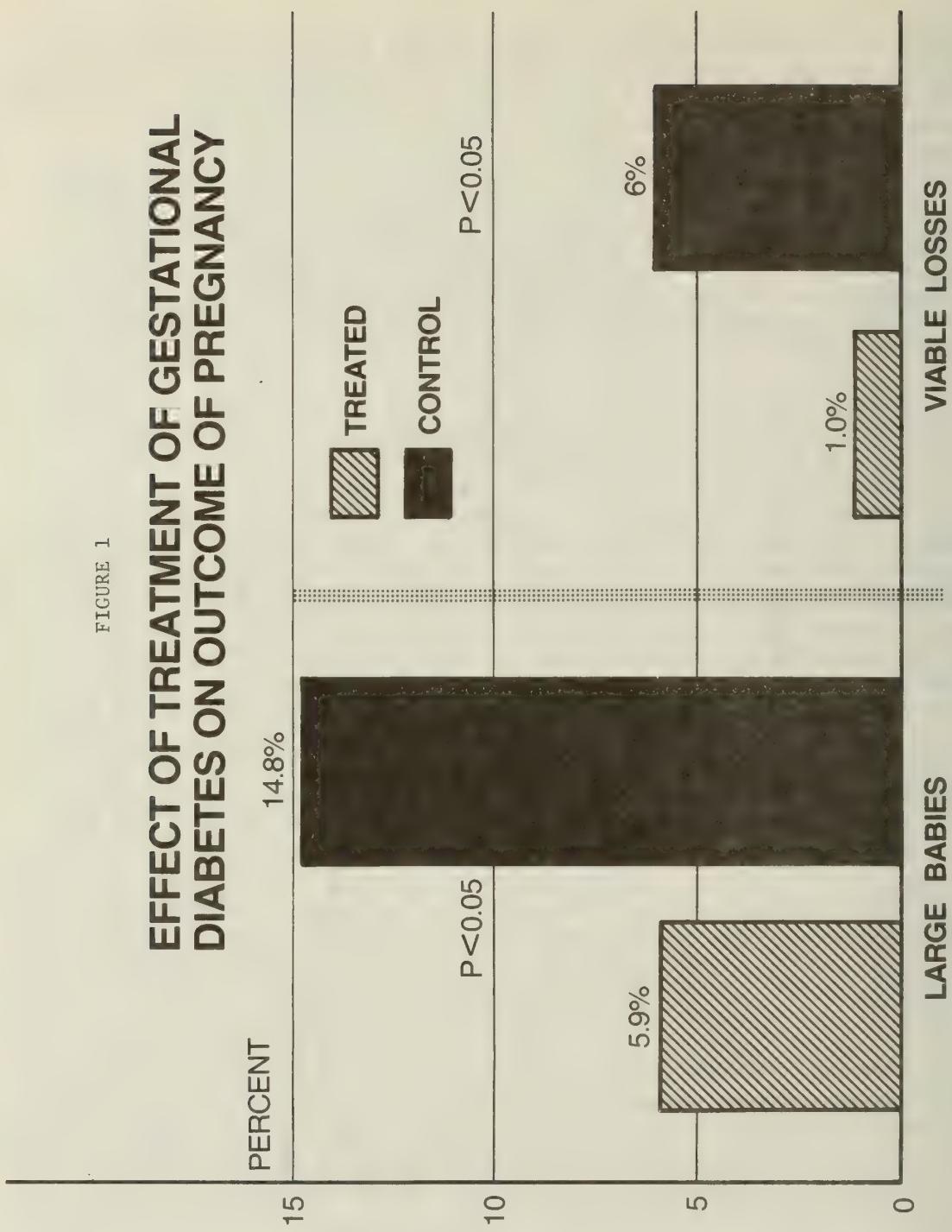
FIGURE 2

**AGE-ADJUSTED PROBABILITY OF HAVING DIABETES, BY PARITY**
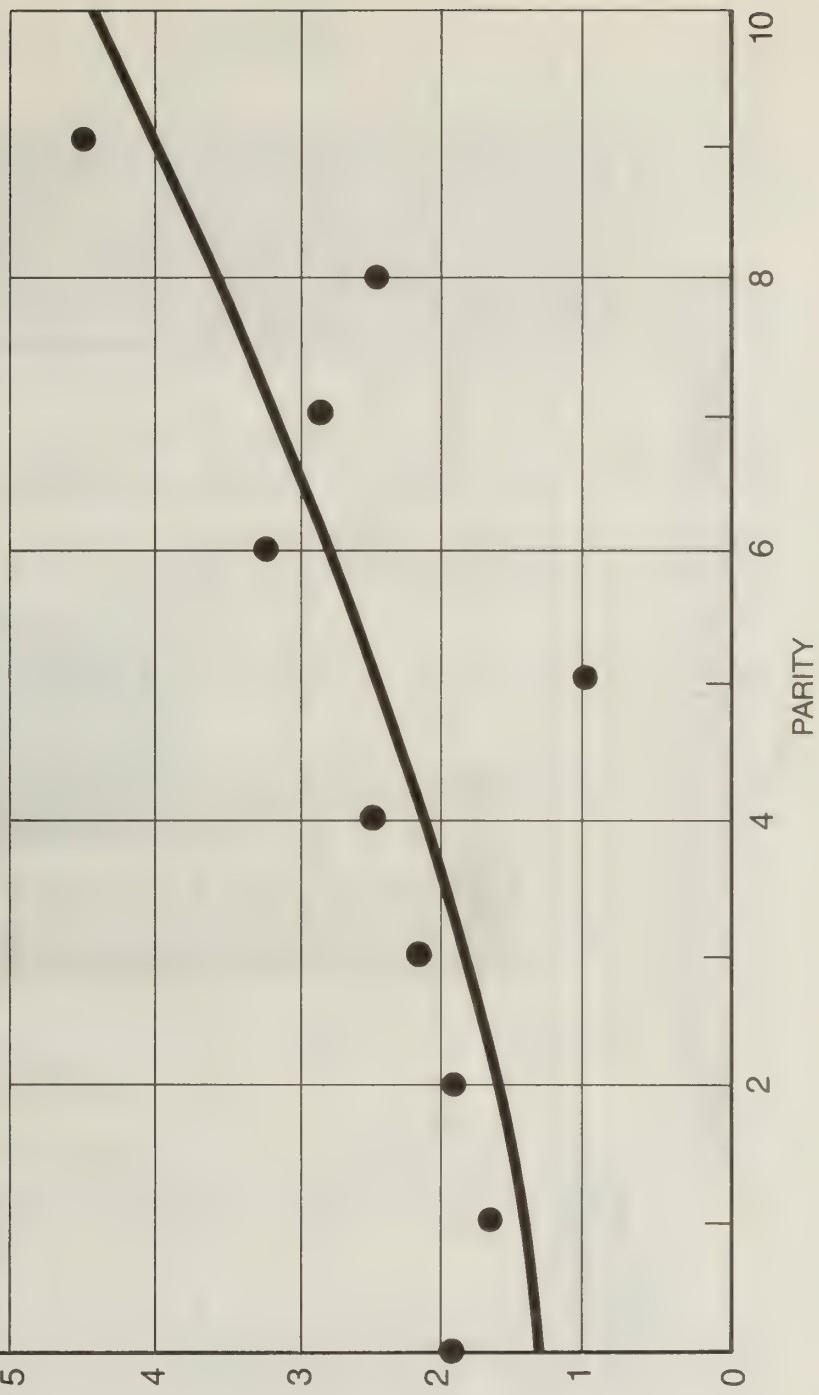
SOURCE: HEALTH EXAMINATION SURVEY, NATIONAL CENTER FOR HEALTH STATISTICS – 1973

233

FIGURE 3

FAMILIAL AGGREGATION OF DIABETES
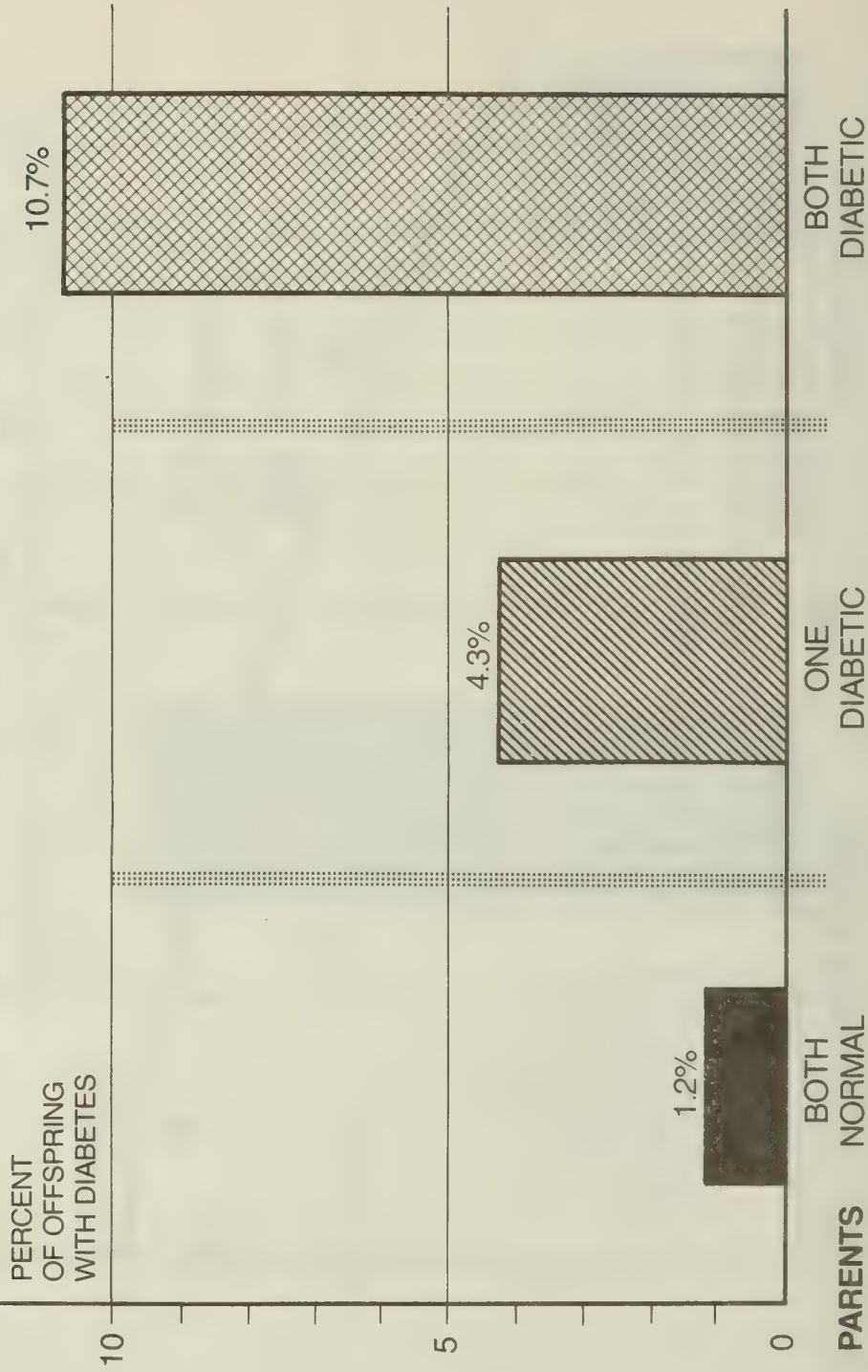
SOURCE: (FROM STEINBERG et al 1969)

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L. PROJECT SUMMARY SHEETS

PROJECT SUMMARY SHEET

PROJECT TITLE: PREVALENCE RATE FOR DIABETES IN PREGNANCY

OBJECTIVE: To determine how many pregnant insulin dependent and
                 gestational diabetic women there are in the U.S.

APPROACH TITLE:

    Epidemiology of Diabetes and Pregnancy

DESCRIPTION OF PROJECT:

    Survey of obstetrical hospitals with adequate casefinding techniques.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Sampling in various geographic locations representative of the
        U.S. population.
    2. Enumeration of total prenatal population in each area for a specified
        time interval.
    3. Casefinding must consist of application of the diagnostic test
        (GTT) to all patients or a predefined random sample of the
        population.

PRESENT STATUS:

    Rough estimates based on local surveys.

INPUT REQUIRED:

    Repeated surveys every 5 to 10 years in order to document changing
    prevalence rate.

PROJECT SUMMARY SHEET

PROJECT TITLE: INDICATIONS FOR GLUCOSE TOLERANCE TESTING IN PREGNANCY

OBJECTIVE: Explore various modes of screening for gestational
                 diabetes with the goal of simplification.

DESCRIPTION OF PROJECT:

The size of the glucose challenge for both IV and OGTT, the fre-
quency of testing required in pregnancy, the most productive time
interval for blood sampling (i.e., time after glucose challenge
and time of day), medical history, glucosuria, and the appropriate
laboratory methodology (whole blood, serum, capillary samples,
quality of assay) should be explored in order to produce an
efficient and acceptable screening mechanism for gestational
diabetes.

KEY EVENTS CRITICAL TO THE
  SUCCESS OF PROJECT:

1. Large prenatal population.
2. Application of tests prerequisites so that sensitivity and
    specificity rates can be obtained.
3. Experience in designing and conducting epidemiologic studies.

PRESENT STATUS:

Good information available for blood glucose levels one hour after
50 gram challenge only. Poor information on most other methods
even though more frequently employed.

PROJECT SUMMARY SHEET

PROJECT TITLE: MATERNAL MORTALITY IN DIABETES

OBJECTIVE: To determine if there is an excess maternal mortality
                associated with diabetes.

APPROACH TITLE:

    Risk of maternity and pregnancy for diabetic.

DESCRIPTION OF PROJECT:

    Collection data from State Maternal Welfare Committees or other
    available sources.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Review of medical records to determine if the mother had dia-
        betes regardless of cause of death, information on death
        certificates, etc.
    2. Establish accurate population denominator and assess the quality
        of prevalence figures for diabetes.
    3. Review deaths from all causes to determine if diabetes was
        adequately included or excluded.

PRESENT STATUS:

    No significant excess mortality is recognized nationally, although
    tentative data supports at least an 8-fold increase.

INPUT REQUIRED:

    Medical record review.

FORM OF RESULTS:

    Identify source of excess mortality for prevention programs.
    Data available for medical education programs.

PROJECT SUMMARY SHEET

OBJECTIVE: To be able to prognosticate more accurately the health
               of mother and infant for prospective mothers with
               diabetes.

APPROACH TITLE:

   Risk factors relevant to pregnancy in diabetic women.

DESCRIPTION OF PROJECT:

   Assessment of relation of maternal age, duration of diabetes,
   vascular disease, metabolic control, type of medical and obstetri-
   cal and pediatric care on perinatal mortality rates, and the health
   of mother and infant.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Centers where long-term care and follow-up will be available.
   2. Sophisticated long-term data storage, retrieval, and analyses.

PRESENT STATUS:

   Description of a few characteristics for a small number of series
   in relation to limited end points such as live births.

FORM OF RESULTS:

   Assessment of identifiable characteristics in relation to health
   of mother and child years later.

PROJECT SUMMARY SHEET

OBJECTIVE: To study the natural history of diabetic retinopathy in pregnancy.

APPROACH TITLE:

Diabetic Retinopathy in Pregnancy.

DESCRIPTION OF PROJECT:

Serial stereo photography, retinal vascular flow with **fluorescein**, hemobarometry, HCS levels, and other techniques to document fundoscopic changes that occur with pregnancy, and possibly identify factors associated with the unpredictable deterioration seen in some diabetics.

KEY EVENTS CRITICAL TO THE
  SUCCESS OF PROJECT:

1. Multicenter, collaborative study.
2. Consider age, duration of diabetes, severity of diabetes (insulin dependent or independent), severity of retinopathy (background or proliferating) as some of the factors for stratification. The experience of the existing Diabetic Retinopathy Study of the National Eye Institute should be used.

PRESENT STATUS:

Poorly documented.

INPUT REQUIRED:

Cases from all major centers for diabetes and pregnancy in the county.

PROJECT SUMMARY SHEET

PROJECT TITLE: DECIDUAL VASCULAR STRUCTURE IN DIABETIC WOMEN

OBJECTIVE: To increase knowledge of placental perfusion by the
                diabetic gravida.

APPROACH TITLE:

Evaluation of uterine vasculature in pregnant diabetic women.

DESCRIPTION OF PROJECT:

Decidual samples obtained after delivery of placenta and studied by
electronmicroscopy immunofluoresence as well as conventional
histochemical stains.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

1. Study of diabetic and control material "blind."
2. Full clinical and chemical records with age, duration of diabetes,
   maternal vascular complication, and diabetes control.
3. Immediate biopsy of implant site after delivery.
4. Expert technical presentation and interpretation.
5. Document the outcome of pregnancy and functional test for
   correlation with placental structural findings.

PRESENT STATUS:

Maternal vascular lesions found in decidua of diabetics as early
as 12 weeks gestation, but not studied extensively.

PROJECT SUMMARY SHEET

OBJECTIVE: Morphometric analysis of placentas of diabetic and
               normal women.

APPROACH TITLE:

   Cellularity of Placentas in Diabetic and Normal Women.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   Availability of placental samples from diabetic and normal women.

PRESENT STATUS:

   It is accepted that the placenta of the majority of diabetics is
   larger and heavier than normal. Winnick demonstrated an increased
   cellularity in the diabetic placenta, but the cells were not
   evaluated. Further study may be pertinent to transfer mechanisms
   and the endocrine function of the placenta.

PROJECT SUMMARY SHEET

OBJECTIVE: To analyze the factors involved in the adaptation of the endocrine pancreas to pregnancy and to evaluate the changes occurring in gestational diabetic or diabetic pregnancy.

DESCRIPTION OF PROJECT:

The histological, biochemical, and functional adaptation of the human maternal pancreas to pregnancy.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

1. Efficient pathological department with light and electron microscopy.
2. Facilities for In Vitro study with biochemical and hormonal techniques.
3. Assessment of the endocrinological status of the mother.

PRESENT STATUS:

No histology or functional studies on maternal pancreas during pregnancy are available since 1932 (Rosenloecher).

INPUT REQUIRED:

Notification of the departments of pathology of maternal deaths. Mechanisms of prompt sampling and handling of pancreatic tissue must be available.

PROJECT SUMMARY SHEET

OBJECTIVE: Congenital malformations in the offspring of diabetics
                documented through prospective controlled studies.

APPROACH TITLE:

    Congenital Malformations in the Child of the Diabetic.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

    1. Collaborative, multicenter studies.
    2. Standardized examination uniformly applied and based on an
        acceptable classification of malformations.
    3. Documentation of diabetes control before and during pregnancy.
    4. Relate the effects of maternal age, duration of diabetes, and
        vascular complications to the presence of congenital complications.

PRESENT STATUS:

    Considerable data available, but documentation inadequate in
    terms of study design.

PROJECT SUMMARY SHEET

OBJECTIVE: Assess the value of insulin treatment on the outcome
of pregnancy in the gestational diabetic.

APPROACH TITLE:

Insulin treatment of gestational diabetes

DESCRIPTION OF PROJECT:

A well established hypothesis that insulin treatment reduces the
fetal wastage among gestational diabetics will be subjected to a
final confirmatory trial.

KEY EVENTS CRITICAL TO THE
SUCCESS OF PROJECT:

1. Collaboration of several large obstetric centers.
2. Random assignments to treatment and no-treatment categories
with stratification according to maternal age (dichotomizing
at age 25).
3. Commence insulin treatment at least prior to the 32nd week of
pregnancy.

PRESENT STATUS:

Retrospective analysis of a large study has set the hypothesis that
insulin treatment beneficially affects the pregnancy of the gestational
diabetic. This result, however, needs independent confirmation in a
prospective trial.

PROJECT SUMMARY SHEET

OBJECTIVE: Cohort study of gestational diabetes for its relation-
                  ship to subsequent overt diabetes.

APPROACH TITLE:

   Natural History of Gestational Diabetes.

DESCRIPTION OF PROJECT:

   Ninety-eight percent of gestational diabetics have a normal toler-
   ance to glucose postpartum. Periodic glucose tolerance testing
   after pregnancy will reveal the patterns in the evolvement of overt
   diabetes. Concurrent measurement of glucose, immune reactive
   insulin, and free fatty acids will reveal the changes in metabolism
   patterns that occur in all stages of developing diabetes.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Unselected population screened for gestational diabetes.
   2. Annual GTTs with analysis for IRI, FAA, and other indexes of
       metabolism.
   3. Existing cohort studies should be favored with every inducement
       to continue.

PRESENT STATUS:

   One major study from an adequate statistical base has been followed
   in Boston. Ideally, this and other ongoing studies should be
   identified and given every support in order to follow their patients
   (i.e., patient enticement, skilled follow-up personnel, etc.). One
   full documentation of an existing long-term study could effect an
   enormous saving in both time and money.

PROJECT SUMMARY SHEET

PROJECT TITLE: CARDIOVASCULAR DISEASES IN EVOLVING DIABETICS

OBJECTIVE: Development of cardiovascular disease in evolving diabetes as seen ideally among gestational diabetics.

DESCRIPTION OF PROJECT:

The low prevalence for cardiovascular disease among women is obliterated in the presence of diabetes. Women with a high risk for overt diabetes offer a unique opportunity for studying the relationship of carbohydrate intolerance and cardiac risk factors to the development of cardiovascular disease. Gestational diabetics fulfill this requirement and results from these subjects can be contrasted with those found among control women with normal glucose tolerance.

KEY EVENTS CRITICAL TO THE
    SUCCESS OF PROJECT:

1. Identify a large group of gestational diabetic and negative control women.
2. Perform periodic electrocardiograms, stress electrocardiograms, segmental blood pressures and other noninvasive tests for cardiovascular disease periodically. Also measure lipoprotein phenotype, document cardiac risk factors, and assess the status of evolving diabetics biannually.

PRESENT STATUS:

Partial information exists and suggests a higher prevalence of cardiovascular disease among gestational diabetics (Boston City Hospital Study).

VIII. Report of the

WORKGROUP ON

THE SOCIOECONOMIC AND PSYCHOSOCIAL IMPACT OF DIABETES

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

Dorothea Webb Puckett, R.N., Ph.D.

VIII. REPORT OF THE WORKGROUP ON THE
SOCIOECONOMIC AND PSYCHOSOCIAL IMPACT OF DIABETES

A. THE SOCIOECONOMIC IMPLICATIONS

1. PURPOSE

The purpose of this report is to formulate a statement of the present problem of diabetes mellitus as it pertains to quality, acceptability, assessment, and availability of care intervention to diabetics from all socioeconomic environments.

2. SPECIFIC OBJECTIVES

An effort will be made to :

    a.   Look at the predictability of outcomes of such health care intervention and to evaluate those outcomes in order to enhance functioning efficiency of care givers.

    b.   Facilitate the necessary change in patient and/or family behavior which would result in maximum care of their diabetic state.

    c.   Encourage institutional and eventual community change to permit enhanced functioning efficiency of care givers in order to promote the necessary behavior change in the individual patient relative to his individual needs and environmental influences.

3. INTRODUCTION

This Workgroup has had the unique advantage of being chaired by a person who brings the perspective of being a black, a nurse, and an educational psychology and community health specialist who has had diabetes since the age of eleven. Consequently, the Workgroup, has, perhaps,

more particularly, felt a keen responsibility to the Commission, to our
nation, and to people with diabetes to look at the problems of those
persons who, because of their socioeconomic status or their special
socioeconomic problems, are not able to avail themselves of the
quality of health care delivery necessary to maintain equilibrium in
diabetes.

The Workgroup has undertaken this unique opportunity and
responsibility realizing that some inherent problems confront us. These
include essentially the time constraint, the fact that this particular
kind of effort with regard to diabetes mellitus has never been concerted
in this fashion before, and that facts and figures which are needed are
not readily available with regard to many of the populations which we are
identifying. Those facts and figures which are available are not
reliable in most cases.

4. IMPACT OF THE PROBLEM

As we attempted to look at the many components of the socio-
economic impact of diabetes, we realized fairly soon that we were describ-
ing a social interaction which occurs between the individual with
diabetes, his environment, a particular health intervention, and some
outcomes. The central concept here is influence. Essentially, how do we
influence patients to change their behavior? How do we influence care-
givers in order to enhance their function and efficiency? How do we
encourage institutional change and eventual community change in order to
enhance the functioning efficiency of the care-givers in order to get
patients to change their behavior?

There is mixed opinion with regard to the financial well-being
of our country. There is no more myth-shrouded aspect of our society
than the pyramid of income and wealth. Throughout the fifties and
sixties we were told again and again by social scientists and public
relations men that the poor were no longer with us or that they were
about to be elevated into affluence by benevolent government programs.
Consequently, we heard incessantly that the big rich were being eliminated
after all these years of confiscatory taxes. We were asked to believe,
in short, that we are part of one big happy middle class society which
is on the march to equality of income and wealth.

Richard Parker's The Myth of the Middle Class, deals effectively
with these and many other myths.

The harsh socioeconomic realities of our present day society
reveal that proverty still does exist (15). In the book, Poverty and
Health: A Sociological Analysis, it is stated that poverty is among the
most familiar and enduring of human conditions. Each generation sees
it differently and judges it according to a particular set of social
values which may be quite unlike those of an earlier era (9).

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The Workgroup wishes to look in stark and unemotional terms at the existing state of health and health service for both the poor and the affluent in our society. Today's affluent American society manifests concern for social as well as physical survival, and our national prosperity has made it possible to provide monies for the study of physical ill health, its prevention, and, in some cases, its cure. As a result, many illnesses have been brought under medical control, and in the process man has become aware that cultural and social factors initiate, influence, or exaggerate illnesses such as diabetes mellitus.

5. STATE OF THE ART

    a. Some Assumptions Regarding the Social Interaction of the Individual, His Environment, Intervention in Health Care, and Their Outcomes

Man is a complex of many individualistic attributes and properties or processes which include age, sex, and personality characteristics. On a higher level of variables are those attributes of social position or status that include occupational choice. There are also variables of social structure such as family and social class. Further, there are attributes and processes of culture that include norms, values, and ideals. Taken together, all of these variables permit one to answer the question, What makes it possible, or impossible, for persons differently situated in a social system to do and be able to do that which will be in their best interest to do? The contributions of social science enable health workers to relate these specific social factors and processes to particular states of health and illness. Our effort, therefore, concerns the concepts of culture and society, socialization into role and status, communication and perceptions, and social class. The ways in which a person thinks, believes, and acts depend largely upon the culture and society in which he dwells. It is within these societal boundaries that his group life and subsequent interpersonal relationships are structured. In these relationships, the person develops personal goals and aspirations that lead him to action. The more a health worker understands the development and consequences of these relationships, the better he will comprehend patient beliefs and behavior as well as his own.

During his entire life, a person has been changed and is changing others through the multiplicity of groups to which he belongs or aspires to belong. He selects some group values and rejects others; he learns new roles and avoids others. Socialization is a constant process from birth to death.

As a person matures, he decides upon a career. If he is to become a health professional, he will undergo not only formal education designed to give him knowledge and ways of applying it, but also an

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informal education to socialize him. As he proceeds through the labyrinth, he will be influenced into new ways of thinking, believing, and acting. As this report will demonstrate, cultural and individual perceptions of health and illness by both patients and professionals are influenced, if not determined, by the roles played by both groups. The differences among social classes often create different health and social problems, and they may require different modalities of patient care. The case worker's commitment to his profession, the organization in which he works, or the patient in his care presents potential conflict for himself and his patients, especially if they cannot find a mutual ground for communication. The patient must also be socialized into the role of a patient. Although the content of socialization may be different for the two groups, as it may be different for the child and the adult, nonetheless the process is the same.

Although man is born into a particular culture, his personality initiates social action that influences the beliefs and behavior of others. Social movements are important because they provide a basic understanding of the ways in which new norms and values are created and acted upon. They illuminate the dynamics of social change which are part of everyday life, the impact of which is felt throughout society.

Trends and social movements within our culture are often created by the desire for change. They begin with a particular ideology justifying the group perspective, and they end with a group action. Such movements may create changes in family structure, the content and process of education, the perceptions, values, and norms of life, and the conceptions of health and illness.

The advice the health care professional gives depends in part on his perception of his function. He may function with purposes in mind that are not related to the immediate needs of any given patient. That is, he may be concerned with efficient care of many patients, involved in research, or preoccupied with professional and organizational mandates that hinder individualistic care. Such a situation can not only hamper treatment, but it also may create role conflicts for the professional. In spite of this some type of dialogue between the patient and health professionals is established and patient care does go on.

Frequently a professional's decision upon a practice-location is colored by many of the factors mentioned above. There are, in addition, many other problems that health professionals must anticipate in order to prevent possible negative consequences, such as language difficulty created by ethnic, cultural, or class differences, or the negative consequences of ignorance and adverse diagnosis or prognosis. Not that patients should be made aware of the latter; but, that the professional having been made aware of them, he is available for a discourse about the consequences for the patient. This in turn requires that the health

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professional be aware of his own basic beliefs, attitudes, and ideology about these adverse conditions. Obviously, if the health professional cannot handle his own anxieties, he will not be able to assist the patient to live in dignity.

The structure of the family, its influences on the individual and its role in health and illness, are primary concerns. Family relationships have enduring significance throughout the life span of the individual. The modes of mate selection and individual family roles not only influence family members but also have broad implications for health care. It is often within the family that the individual discovers ways in which to solve everyday stresses and strains. The ways in which he learns to handle these problems influence his ability to withstand more serious emotional and physical stresses which can create or contribute to a variety of illnesses. This modality of action determines how he can manage the potential and real crises of illness throughout the family life cycle.

Consequently the health professional must not only be concerned with the individual patient who has sought or been brought to his care; he must consider the family constellation and the mutual relationship of patient to family. Information regarding the diagnosis, progress, and prognosis should be communicated to both the individual and his immediate family or other significant people. In many instances, the family, whose members are of crucial importance in the patient's care, rehabilitation, and resocialization into society, is the last to be informed by health professionals. Not only is this important, but in many instances the care of the patient requires the involvement of both the individual and his family in the decisions regarding his fate.

If the health professional is aware of some of the socio-cultural dynamics of individual action, ways may be found for prevention of serious hazards or at least earlier treatment and care. This is true because a person's behavior is based on what he takes into account of his own goals, of others' expectations of him, and of his image of what his action will mean to himself and others. This action may be centered around a particular event or around a series of social situations. If he is ill, he may accept without question any information given by those who are close to him, or he may accept information only from particular categories of health workers. He may seek general information or solely that which is specific to his perceived problem. Once engaged in treatment, he may question the treatment modality, intervene in the treatment plan, or manage his own care.

Each individual has his own comprehension of the illness, health, and the professionals and agencies that provide care. Everyone has his own terminology for defining illness and care which may or may not coincide with that of health workers.(9) The following are possible perceptions and actions of particular individuals:

1. Understands the health problem but modifies it to fit his own life style.

2. Understands the health problem but rejects it.

3. Understands the health problem and accepts professional treatment.

4. Does not understand the health problem but seeks help for a solution.

5. May neither understand the health problem nor seek help for its solution.

b. The Individual's Action Depends Largely On His Understanding of the Situation.

What is the path of patienthood? If the individual becomes ill and decides to seek medical care, he is confronted with a variety of new situations and problems. He does not become a patient simply by becoming ill or being hospitalized; rather, he learns this new role. Both he and the health workers are then faced with problems of stress, anxiety, fear, and possible death. The implication of these problems may vary depending on the cultural and social backgrounds of those involved in the care process. Differences in perception of these problems may facilitate or hamper the patient's ability to adapt to his new situation and participate in his treatment and care along the way to rehabilitation.

The health professional has the responsibility to help the patient to strive to understand clearly what he is expressing. This implies that all communication transpires on the patient's level, which in turn depends on the social variables that impinge upon the patient's perception. The health worker must also endeavor to become aware of factors lying beneath the surface of the verbal notations, and these factors include psychosocial problems such as the patient's shifting roles and changes in his self-concept and in family demands.

The health professional must be cognizant of the fact that patients try to maintain a self-image and life style unchanged by disease. The patient often tends to see himself as unaltered by disease even though he may have many changes in his way of life. The extensive adjustments he makes in response to his illness are determined by his sense of what is adequate for himself. Such adjustments include initially making his own diagnosis and instituting his own care based on previous or readily available experiences. The health worker thus has an additional responsibility to disseminate accurate information to a public audience.

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Problem solving techniques, if properly used, allow the health worker to deal with everyday and individualistic contingencies that confront him. This technique is not sufficient, however, for the development of a theory of health care and practice which is essential to coping with health problems on a large scope.(9) This problem belongs to the realm of research.

Although the influences of psychological and social factors of illness have long been recognized, relatively little has been done to study the extent of these influences on diabetes. Research into these psychosomatic influences has not traditionally been done because the expertise and manpower have not been readily available, there is little standardization of tools needed to collect this data, and this is difficult information to secure.

Most sources of morbidity data, except for reported hospitalizations, do not seem to be satisfactory, primarily because of unreported diseases and undiagnosed illnesses. Furthermore, medical criteria used for verification of reported morbidity have been observed to be somewhat lacking in reliability. Unfortunately, the reliability and validity of the evidence of class differences in morbidity statistics are inconclusive, partly because many researchers either fail to analyze their data by class factors or fail to report their findings related to class.

Despite the inadequacy and lack of reliability of existing morbidity data for purposes of ascertaining class differentials, the available evidence does suggest the existence of such class differences. On the one hand, actual medical care and the accuracy in reporting such care, as well as cooperation in household morbidity surveys and health examinations, do seem to be directly related to reported socioeconomic status. Therefore, community health surveys and examinations tend to favor the more easily observed attendant conditions among the middle class.(12) On the other hand, the poor tend to go to public clinics where their diagnoses are recorded; and much of the reported morbidity data relies on the records of public facilities. Middle class patients are more likely to see private doctors who do not always note the complete diagnosis and are prone to omit socially stigmatizing diagnoses. Moreover, few studies in the field of health care, other than community surveys, include data from private practitioners having middle class patients. Thus, class differentials in the utilization of public facilities and the labeling of illnesses, together with the reliance of much of the reported morbidity mainly on public records, would seem to increase the observed morbidity of the poor.

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c. <u>Other Limitations and Variables</u>

Many subpopulations need to be focused upon to enhance the care
of their diabetes. Most of these populations have been traditionally
neglected. Included among these are: the diabetic adolescent; the
person with diabetes who lives in a rural area; the diabetic patient who
is poor and lives in an urban area; the American Indians, who as a
group, have had long neglected health care; and the non-English speaking
Americans. Many reports and much documentation exist to support the
need for new approaches to the health problems of these subpopulations.
Little has been done to implement those things which have been suggested
in previous documentation and little of this documentation is related
to diabetes mellitus as a specific health problem. The Commission has
heard in various parts of the country supporting documentation of the
socioeconomic problems of specific populations. The major statements
of this nature were heard in Seattle and Chicago. (See public testimony.)
Since much of the support for health care is based upon statistics, our
efforts, for lack of better data at this time, will reflect the superim-
posed problem of diabetes upon existing statistics and reports.

As can be seen from the testimony given at the hearings held by
the Commission, this Workgroup has had some difficulty in securing
sufficient and representative public testimony regarding its very basic
issues. Dr. Juanita Archer of Howard University has documented that
the diabetic patients who are the focus of our attention in this report
frequently have to lose time and money from work in order to attend
diabetic clinics. These people really are not affiliated with diabetes
organizations or in some cases even aware that a Commission exists which
is looking into the problems of the diabetic patient. Taking these
things into account, channels other than the traditional public testimony
avenue have been used by the Workgroup to secure public opinion regarding
health care delivery for people with diabetes.

An indication of the limitations upon dealing effectively with
the concerns of this Workgroup can be found in Public Law 93-354, the
"National Diabetes Mellitus Research and Education Act," which makes
little provision for socioeconomic issues. Section 3(e) of the Diabetes
Act states, "The Commission shall formulate a long-range plan to combat
diabetes mellitus with specific recommendations for the utilization and
organization of national resources for that purpose. Such a plan shall
be based on a comprehensive survey investigating the magnitude of
diabetes mellitus, the eipidemiology, and <u>its economic and social con-
sequences</u> and on an evaluation of available scientific information
and the national resources capable of dealing with the problem." This
is perhaps the only place the word socioeconomic, or economic and social
consequences, is used in Public Law 93-354. We believe that this illus-
trates the emphasis which has traditionally been placed upon socio-
economic issues related to health care problems. Nonetheless, there are
several portions of the Act which have implications for research into
the socioeconomic issues involved with diabetes, and it is the hope of

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the Workgroup that research done as a consequence of this Act will indeed include research into the socioeconomic complications. Programs should also be established to evaluate, plan, and disseminate knowledge related to research and training in diabetes mellitus and related endocrine and metabolic disease. Hopefully part of this research will be into the socioeconomic dynamics of the health care delivery system.

At the risk of being repetitive, this Workgroup believes that diabetes can be complicated by socioeconomic problems; and it is the hope of this Workgroup that such centers as are provided for by Public Law 93-354 will be sensitive to the needs of patients with problems related to assessability, availability, and acceptability of self care.

d. Some groups with Outstanding Socioeconomic Problems

From data reported to the Bureau of the Census in March 1964,it can be inferred that one in seven of all families of two or more and almost half of all persons living alone or with relatives have incomes too low to enable them to eat even the minimal diet that can be expected to provide adequate nutrition and still have enough money left over to pay for all of the other living essentials.

Who are the people who tug at the national conscience? Are they all social casualties visited by personal misfortune, like the woman left alone to raise a family? Are they persons who find little opportunity to earn their living, like the aged or the unemployed? Or are they perhaps mainly members of ethnic minority groups who are living out the destiny of their years of discrimination? These groups, to be sure, are among the poorest of the poor, but they are not alone.

Many of our aged have inadequate incomes, but almost four-fifths of the poor families have someone under age 65 at the head and nearly half of all individuals classified as poor have not reached old age.

Non-white families suffer a poverty risk three times as great as white families do, but seven out of ten poor families are white.

And finally, in our work-oriented society those who cannot or do not work must expect to be poorer than those who do. Yet, more than half of all poor families report that the head currently has a job. Moreover, half of these employed family heads, representing almost 30% of all families called poor, have been holding down a full-time job for a whole year. In fact, of 7.2 million poor families in 1963, one in every six (1.3 million) is the family of a white male worker who worked full-time throughout the year. Yet, this is the kind of family that in our present society has the best chance of escaping poverty.

All told, of the 15 million children under 18 who are counted as poor, about 5.75 million were in the family of a man or a woman who had a full-time job during the year 1963 (8).

The following comments are based upon a publication of the Environmental Protection Agency which addresses our urban environment and our most endangered people (17). Whatever the hope, be it opportunity or stimulation, that brings people to urban complexities--whatever the success or failure that keeps them there--130 million Americans share a deteriorating urban environment. For each of them, whether rich or poor, white or black, suburbanite or city dweller, there are increasingly heavy physical burdens from environmental depreciation. These physical burdens are imposed by air pollution, noise, pesticides, and other toxic substances. While these are borne by all, they fall most crushingly on the persons of our inner cities.

These physical conditions of poverty can create breaking-point tensions, and when environmental stresses are added, the problems of the inner city poor are greatly compounded. These compounded and complex problems include that of obtaining health care in a central city area. One hundred thirty million Americans now live in urban areas. Of these, nearly eight million are central city residents existing in poverty--4.5 million white and 3.1 million black. Many people have an income much lower than the poverty level, which is officially defined for the non-farm family of four as having an income of less than $3,968 per year. Approximately another eight million near-poor have incomes slightly above the official poverty level, and while they are not counted in the statistical eight million poor, they nonetheless suffer a similar fate. Contrary to common beliefs, the urban poor are not mostly black; in fact, they are predominantly white. The mistaken belief probably stems from the fact that 25% of the black population lives in poverty. The age distribution of the eight million urban poor is also significant. Three million are under age 15 and nearly two million are over 65 years of age.

The mental and physical consequences of a disease are intensified by certain factors intrinsic to poverty level subsistence, such as: 1) unemployment with the resulting lack of money, lack of self-respect and dignity, poor housing which includes inadequate, decaying, or infested buildings; 2) overcrowding of residences with more than one person per room. Without the money to obtain adequate food, clothing, housing, medical care, and education, the urban poor suffer from under-nourishment, malnutrition, high disease prevalence, shorter life spans, and the inability to break out of the cycle of poverty.

The major chronic condition referred to in the Environmental
Protection Agency publication is heart disease. Essentially it says
that heart disease is a major chronic condition which adult poor suffer
along with the rest of our adult population. However, if one is poor and
black, the chances of suffering from hypertension are three times greater
than for a white with a family income over $10,000. Other chronic con-
ditions which afflict the poor include emphysema and other respiratory
diseases, hearing, and sight impairment. Further, persons who have a
family income of less than $3,000 per year are subject to a substan-
tially higher incidence of one or more chronic conditions. Think of the
implications of this statement for the chronic condition of diabetes
mellitus. Limitation of activity due to a chronic condition occurs four
times more in the lowest income group than in a family group with an
income of over $7,000.

Lewis Furman summarizes the problem of poverty by attempting to
demonstrate that the subsistence level definition of poverty is arbi-
trary, circular, and relative. The definition of poverty which is based
on nutritional requirements is dependent not only on expert definitions
but also on actual levels and patterns of living. Thus, no extrinsic
standard to measure food adequacy is available and the subsistence
definition of poverty is, therefore, circular. But this procedure imposes
a number of arbitrary judgments which rob the nutritional approach of its
claim that it is based on scientific rigor with minimum attention to
value judgments. To take account of customary behavior requires that we
know in advance the relevant income group which distinguishes the poor
from the non-poor. Thus, the procedure for measuring poverty is based
on a circular argument from which it cannot retreat. The result is that
those who hold different value judgments concerning how stringent or
lenient the poverty standards should be can use the same data to demon-
strate that poverty is either a significant or a trivial problem. All
of the procedures in establishing a trade-off between consumption stan-
dards and an expert judgment have an arbitrary quality which can be
challenged by those who wish to see the standards of poverty defined more
harshly or more leniently. On the other hand, the criterion that budgets
should be most economical forces the expert to accept an unrealistic
assumption of a no waste budget and extensive knowledge in marketing and
cooking. An economical budget must be based on knowledge and skill
which is least likely to be present in the low income groups with which
we are concerned. The result is that a stubborn and continuing ambiguity
between primary and secondary poverty is built into the procedures by
which the minimum nutritional standard is determined. If we cannot
distinguish between the capacity to consume and the adequacy of the
resource base for consumption, there is not an independent standard for
questioning or revising expert judgment. Bear in mind that diabetes is
a nutritionally related disease.

Almost every procedure in the subsistence level definition of poverty can be reasonably challenged. The estimates are based on the consumption pattern of the entire low income third of the population instead of upon subgroups of this population. The estimates of nutritional needs take age and sex into account but not physical activity. Average price and average consumption, rather than actual behavior, are used as the standards for constructing low cost food plans. The economy food plan is an arbitrary derivation of the low cost plan. Consequently, we have to conclude that subsistence measures of poverty cannot claim to rest solely on a technical or a scientific definition of nutritional adequacy. Values, preferences, and political realities also influence the definition of subsistence. Yet, once a biological definition is abandoned and actual consumption is taken into account, no absolute measurement of poverty in substantive terms is possible. Registered dietitians have reiterated to the Commission that income should be taken into account when planning for diabetic meals.

Consider how devastating diabetes could be to an elderly person. Incomes of elderly persons are not always adequate for basic needs, and only a small proportion have enough security to absorb the cost of unexpected crises such as a chronic disease. The effect of a generally rising income and considerably more participation by the public sector unfortunately has not extended to all elements in the population. The elderly poor are a sizable group and they are found in urban and rural areas alike.

The urban poor, who are largely concentrated in the older areas of central cities, are uniquely and pathetically disadvantaged. Because they rely on money income as a means of obtaining an adequate amount of the needed and desired articles of consumption, they are extremely sensitive to changes in income and prices in both an absolute and a relative sense. Furthermore, they have little freedom to maintain their own incomes. Their economic fate rests, sometimes wholly, on the decisions made by legislative bodies and administrative agencies regarding both the minimum standard of living for which they should be provided and the types of persons who are eligible to receive assistance. Few employment opportunities are available for the elderly person of low skills and meager educational attainment who reside in these areas. Private pension programs that depend directly or indirectly on past earnings do not apply to most of these persons, and non-cash income supplements are minimal; therefore public assistance and social security are the two programs that provide the bulk of whatever income is received.

It is the elderly person who has earned and saved little during his lifetime who faces the greatest financial deprivation and uncertainty in his later years and the elderly residents of a central city area often find themselves in this predicament. They are among the

first victims of early layoff and mandatory retirement; they often have the disadvantage of low skill and educational attainment; and they are increasingly of minority status. These are related factors which militate against their being in a position of financial independence. Hence, they are required to live within the stringent budgetary limits associated with public income maintenance programs. Just as such elderly persons as these who have diabetes are frequently not able to purchase the necessary supplies or make payment for the necessary health care interventions for the optimal care of their diabetes, many other poor and elderly persons who live in close proximity to them also cannot afford the necessities of optimal health care.

It has come to the attention of this Workgroup that those persons who are institutionalized frequently do not receive the care needed for equilibrium in terms of their diabetes. Two prime examples of this kind of institutionalization are nursing homes and prisons but we are sure that many other such examples exist. The report of the President's Commission on Rural Poverty in 1967 addressed itself to the health status of the rural poor. This Commission was profoundly disturbed by the health problems of low income people in rural America. Nowhere in the U.S. was the need for health services so acute and nowhere was it so inadequate. Even today, the statistical evidence is overwhelming, yet the statistics barely suggest the inequity and the discrimination against the rural poor in medical and dental care in modern health services.

We have failed miserably to protect the health of low income people in rural areas. The health service that they get is not only inadequate in extent, but it is also seriously deficient in quality, it is badly organized, it is underfinanced, and it is rarely related to the needs of the individual or of the family. Such health service as exists is too often discriminatory in terms of race and income and heedless of the dignity of the individual. The President's Commission on Rural Poverty further stated that it is strongly of the opinion that comprehensive and continued health service of the highest quality should be accessible to all Americans regardless of race, income, and place of residence.

Limitation of activity due to chronic illness is obviously more prevalent among the poor than among the rich. The results of this consequence of chronic illness are even more pronounced when they affect the person's ability to work, to do housework, or to go to school. Regardless of income, rural residents, and essentially the elderly, are much more likely to have disabling and chronic health conditions than are their urban counterparts. Rural persons also have higher rates of injury than do urban residents, they have more days of restricted activity, and they lose more days from work due to illness and injury than their urban counterparts.

Because the urban poor do not have easy access to appropriate health services early in the illness, they have much greater disability later. Available data on services provided by physicians and dentists

clearly show that the poor are less likely than those with higher incomes to receive adequate medical care and the lack of medical care is most acute among the children of the poor.

Regardless of income, rural farm residents average fewer physician visits per person (consultation with a physician or service provided by a nurse or other person under the physicians' supervision) than rural non-farm or urban residents. Rural residents, especially the children of the rural poor, are less likely to have to use the services of a physician then their urban counterparts, and relatively more rural residents than urban residents have never seen a physician.

e. Health Manpower and Facilities

The scarcity of health manpower and facilities in the low income rural areas is alarming and is not likely to be corrected overnight. Although about 30% of our population still lives in rural areas, only 12% of our physicians, 18% of our nurses, 14% of our pharmacists, 8% of our pediatricians, and less than 4% of our psychiatrists are located in rural areas. Because of continued population growth, advances in medical knowledge, and overall improvements in the opportunities of people, the demands for health services and, therefore, for health personnel to provide the services will continue to increase. Shortages of hospital beds and of high quality extended care facilities, such as nursing homes and other homes for the aged, chronic disease hospitals, and geriatric hospitals, also are unlikely to be corrected in a short time. Needless to say, the strain will be felt most in rural areas of the nation. The preceding information has strong implications for the placement of potential diabetes centers.

Although quality hospital care cannot be measured solely by the number of beds, we do know that the size of the hospital, to some extent, reflects the services available. The large hospitals are better staffed with technical personnel and specialists and are generally better equipped. But rural people have to depend largely on smaller hospitals. In these small hospitals in the outlying areas, organized free outpatient departments are seldom found, not to mention diabetic or endocrinology clinics.

Many of these rural patients are elderly and suffer from physical illnesses such as diabetes which result in psychiatric disorders. Often when these physical illnesses receive appropriate medical treatment, the psychiatric disorders disappear.

6. SUMMARY AND CONCLUSION

In summary, the recommendations for possible approaches to health care delivery are essentially the same as those made by the other committees of this Commission. Our major concern has been to stimulate

an awareness of the socioeconomic problems in this country as they relate to diabetes mellitus.

A fundamental component of medical care of high quality is the constant and unfettered development of research studies in natural science, clinical medicine, social and economic aspects of disease, preventive methods, and health administration (5). The many unsolved problems in prevention and control of diabetes and in methods of medical care organization require the fullest possible research activity on the part of persons involved in the service program as well as those devoting full time to investigative work. Diabetes centers should promote a better quality of care by providing opportunity within the program for professional and administrative personnel to utilize the facilities for research purposes.

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B. PSYCHOSOCIAL IMPACT OF DIABETES MELLITUS

1. INTRODUCTION AND PURPOSE

Psychological and social factors have long been recognized to influence the course and outcome of many medical illnesses. Diabetes mellitus is generally considered to be one such disease. Diabetes requires the patient to be directly responsible for the continuous daily management of his disease. In addition, the diabetic patient is usually compelled to include in his treatment plan, his friends, family, and society as well.

These psychosocial factors may, therefore, affect the diabetic patient by modifying his behavior or actual physiological events. This sets the stage for the following type of interaction to occur:

Psychological   Social
     factors   factors

Diabetes _____ Outcome
             Natural History
             Treatment
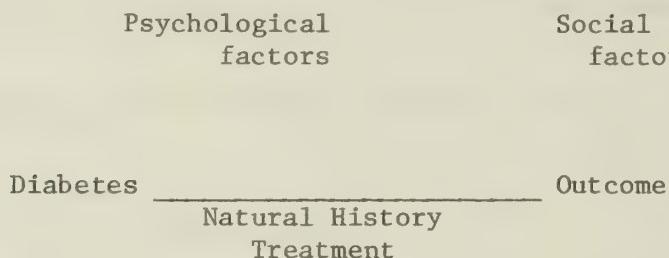
There has been, however, comparative little research directed towards elucidating the interrelationships between the psychosocial situation and the natural history of diabetes. As a result, it has been difficult to implement satisfactory therapeutic approaches to modify the adverse consequences of even the most elementary psychosocial phenomena confronting the diabetic patient.

Several factors have contributed to the lack of emphasis placed on the psychosocial concomitants of diabetes mellitus. The discovery of insulin was, as first, widely regarded as a complete cure, and for more than 20 years treatment consisted of little more than administration of an appropriate dose of insulin. This clinical impression inhibited further consideration of research into factors other than the purely physiologic. This emphasis was enhanced by the commonly expressed skepticism of the biologically-trained physicians towards the findings of psychologically and sociologically oriented researchers.

When the importance of the social and psychological factors in diabetes was finally recognized, other problems became apparent. Psychosocial data were found to be difficult to collect and evaluate. Widely accepted and empirically validated investigational methods were

not easily applied. Interviews, social surveys, and written tests
each had limitations, and the relative lack of trained investigators who
understood both the social sciences and the medical disease - diabetes -
was even more critical. Obviously, no psychosocial investigations of
the diabetic patient could be complete without a knowledge of both
disciplines.

To date, the information available has only occasionally been
translated into meaningful treatment programs for diabetic patients and
their families.

Considering the previous statement, the purposes of this report
are to:

      a. Re-emphasize the importance of psychosocial factors as
          they influence the course of outcome of diabetes upon
          the person with that disease.

      b. Identify some of the more critical psychosocial factors
          confronting people with diabetes.

      c. Recommend approaches to modify the impact of psychosocial
          factors on the diabetic patient.

2. IMPACT OF PSYCHOLOGIC FACTORS ON THE DIABETIC PATIENT

The hypothesis that emotional factors influence the clinical
course of diabetes is often stated by diabetologists; however, research
supporting this concept has largely been confined to the publication of
suggestive case histories. Few prospective studies of large groups of
diabetic patients have included consideration of psychological factors.
Further, laboratory experimentation on the effect of stress on the
diabetic patient is rare.

Several types of interaction between the emotional state of the
patient and the course of his disease have been suggested:

    a. Psychological Factors in the Etiology of Diabetes

From the time diabetes mellitus was first recognized as a clinical
entity, various investigators have suggested that acute or chronic emo-
tional stress might either cause diabetes in a previously normal person
or precipitate diabetes in a genetically predisposed individual. In
spite of many highly suggestive case histories, investigation of this
hypothesis has never demonstrated such a cause-effect relationship. It
appears unlikely that emotional stress alone can produce permanent
diabetes mellitus in a totally nondiabetic individual.

b. Psychological Factors Affecting the Metabolic Status in Diabetes

In the normal person stressful life situations may induce hormonal changes resulting in significant variations in blood sugar. Similar effects have been observed in diabetic patients.

Indeed, the juvenile diabetic patient has long been identified as having much wider variations of blood glucose and often significant ketone production during stress situations.

The degree of psychological stress necessary to induce a specific metabolic alteration is not exactly known. Most studies have found that situations to which the diabetic patient may respond metabolically are unpredictable. What may appear to the observer as a major life crisis may be passed with comparatively little change in the degree of control, while other seemingly innocuous events may produce major metabolic up-heavals, i.e., ketoacidosis. It has been suggested that only part of the diabetic population is susceptible to alterations in control by emotional events; thus, some have divided the group into the stree-responsive and non-stress--responsive. It is clear that for many diabetic patients life situations characterized by difficulty with family, occupation, and finances produce significantly more stress and, therefore, more sus-ceptibility to poor diabetic control. On the other hand, patients whose lives are relatively serene and secure are often more stable in their diabetic control.

c. Psychological Factors Affecting Compliance with Diabetes Therapy

It has been clearly established that psychological factors have a major effect in influencing patient motivation in the repetitive daily tasks of self-management. Several studies have shown that the single most common precipitating factor in diabetic ketoacidosis is the omission of insulin and that many of these patients who neglect to take insulin have specific emotional disturbances which directly lead to the omission. Indeed, certain patients seem to use the diabetic state as a weapon against themselves, their families, or their environments. The adoles-cent diabetic patient seems especially prone to this specific behavior.

d. The Diabetic Personality

There have been a number of attempts to characterize the person-ality of the person with diabetes. The problem has been to distinguish between personality traits antedating the onset of the disease and those which develop as a result of the disease. Because of the difficulty of obtaining satisfactory data about the premorbid personality of a diabetic patient, conclusions in this area are largely unreliable.

e. Conclusion

It is apparent from the literature that there are fundamental gaps
in our knowledge of how psychological events affect physiological mech-
anisms. At the present time, no general conclusions can be made regarding
these important factors influencing the diabetic patient. Problems of
methodology seem to be, as yet, unsolved; and most studies to date can
easily be criticized on a variety of grounds.

3. IMPACT OF SOCIAL FACTORS ON THE DIABETIC

In addition to emotional stress, social interactions can interfere
in the diabetic patient's management-control process. These interactions
may either decrease motiviation to comply with self-management or elicit
emotional distress, thereby interfering with diabetic control.

While not all social factors can be discussed in this paper, it is
necessary to reemphasize a few of the most obvious problem areas:

a. Interactions of the Diabetic Patient and the Family Unit

The immediate family provides the closest and most continuous
social contact for the person with diabetes. Unfortunately, there has
been virtually no serious investigation of the effect of diabetes on
family interrelationships or the effect of the family on diabetic
control. Clearly, attitudes of the immediate family, either supportive
of non-supportive, will influence the emotional well-being of the member
with diabetes. This may be critical in altering motivation for good
self-care. Experience has shown that many times diabetic patients
either ignore family pressures regarding management or, less often, allow
the family to assume total responsibility for all decisions relative to
the disease.

While it is important for the family members to be aware of, and
help in, the management of diabetes, the extent to which this is
actually done varies greatly depending on family structure and specific
interrelationships.

In most instances, little attempt is made by the health care
provider to reasonably integrate the family into the management program.
It is common for the family member who controls possibly the single most
important aspect of management - diet - to be completely ignored in
dietary education. Even when this family member is included in dietary
education, he may consciously attempt to ignore or minimize the
importance of diet so as not to "alienate" the individual with diabetes
or "penalize" the rest of the family.

Specific psychologic family structures seem to be correlated with
poorer outcome. Prominent among these is the family with a single adult

psychiatric illness, alcoholism, drug abuse, or the presence of other chronic diseases.

Traditional medical practice, though long paying tribute to the concept of treating the diabetic patient in his social environment, has almost exclusively focused on the individual. As a result, the information available for analysis of this problem has been, and continues to be, minimal. Recent investigative efforts deal almost exclusively with diabetic children whereas this problem clearly extends to families of all diabetic patients.

b. The Childhood Diabetic Patient

One of the most critical factors in the life of the child who has diabetes is the response of the parents.

Often parents perceive diabetes to be a disaster for the family. Parents who are able to take serious infectious disease or injury in stride seem to regard diabetes as equivalent to the death of a child. It is common for parents to blame each other or relatives for the defect in their child when they learn of the possible role of heredity in diabetes.

Despite their feelings, daily management of the diabetic child falls most heavily on the parents. All too frequently the parents are not adequately counseled by the health team regarding the natural history of diabetes and, more importantly, how they can assist with the child's management. Often the responsibility falls on the mother alone with no participation by the father.

Standards of control demanded by both physician and parents are frequently unrealistic. The child invariably falls short of these expectations, leading to parental frustration or frank anger directed at the diabetic child.

Parents of diabetic patients frequently meet together and compare physician management of their children, and become angry with their physician if their child's control isn't as perfect as the next. It is not uncommon for parents to "doctor-hop" in hopes that one physician will know the perfect combination of insulin and diet for their child. The child ultimately suffers the emotional and medical consequences of this behavior.

c. Interactions With Peer Groups

Friendship and social interaction with peers is one of the most important aspects of life. Because of a desire to be no different from other members of their peer groups, many people with diabetes do not tell even close friends about their disease. They fear the possible

rejection and humiliation that frequently accompanies the revelation. This secretiveness frequently spreads to other areas until the person can no longer allow himself the luxury of being close to anyone.

This sequence occurs in the other direction as well when the person reveals his problem (9). It only requires a negative reaction from a few peers before he begins to revise his self-image downward and become secretive. Similar rejections are frequently encountered by persons with other handicaps. The diabetic patient can, and does, avoid this type of interaction by distancing himself from his peers or denying the existence of his disease. Frequently, the person will seek out other peer group members who also have diabetes for support because they have common problems.

d. School System Interactions With the Diabetic Patient

Even in the most depressed areas of our society, a person in the formative years spends the greater part of his time in an educational system. Indeed, education for many people lasts well into adult life.

The problems facing a person with diabetes each day in a school system are extremely multifaceted. Some are simply mechanical -- if a child with diabetes needs a mid-morning or mid-afternoon snack, and there is no recess period scheduled, he must either try to sneak his snack, try to eat prior to class, request permission from the teacher to eat in class (a universally prohibited act), or not eat and risk a reaction. Requesting permission for snacks, available to no other child, announces his disease publicly every day.

A second problem arises with regard to the teacher. Even the very young child quickly learns to self-manage his diabetes. He is expert in a way that his teacher can never be. This can create resentment on the part of the teacher, who feels that his authority is being undermined if the child dictates any action. He may attempt to set rigid rules which may, occasionally, be totally unsuitable for the diabetic child. When the child challenges these rules in hopes of preventing a meta-bolic disaster, the teacher suspects that the child is trying to manipulate the classroom situation.

On the other hand, the extra latitude allowed the diabetic child is a responsibility for which he may not be ready. He may indeed try to use his diabetes to avoid tasks which he does not like. He may be tempted to feign reactions to gain attention. More commonly, however, the diabetic child avoids the steps necessary for proper control for fear of being identified as being different.

The school system frequently promulgates special rules in a mis-guided attempt to help the diabetic student. Classically, the diabetic student may be kept from participation in sports because the coach fears

some adverse reaction. Usually, this fear is based on ignorance of diabetes. There is currently no national program of education regarding diabetes and the student which is available to teachers or school systems.

Finally, realistic career counseling of students with diabetes does not exist. All too frequently career counselors set goals inappropriately high, or worse, limit career choices, thereby discouraging self-fulfillment.

From this, it is small wonder that most physicians dealing with young patients with diabetes find emotional upheavals affecting diabetes control secondary to those originating in school experiences.

e. Employment and the Diabetic Patient

People with diabetes have long been identified as being victims of diffuse employment discrimination. This is based upon the employer's unrealistic ideas of what diabetes is and what a person with diabetes can do. It is, however, important to recognize that some jobs exist that should exclude people with diabetes by virtue of the job creating danger for themselves or others. However, it must be emphasized that most people with diabetes can do most jobs.

Employers in general are reluctant to hire people with diabetes for a number of reasons. Some have no idea about the nature of diabetes and fear that diabetes might be contagious or that the person might suddenly have a seizure of other undesirable behavior. Some think that other employees might not wish to work with a person with diabetes or that there will be excessive time lost due to illness. If the business has an employer-supported health insurance plan, there may be a desire to avoid the higher premiums demanded by insurance companies as a result of diabetic employees. Often an employer believes the diabetic employee will use his illness as an excuse to avoid certain tasks. Whatever the reasons, the fact that people with diabetes are discriminated against in employment situations is clear.

As a result many people with diabetes have adopted the strategy of disguising the fact that they have the disease. They are careful to disclaim diabetes in pre-employment interviews and they avoid physicals and blood tests except on days when they are in good control. After being hired, such a person with diabetes continues to keep his illness a secret from his fellow workers. By doing this, he does place himself at some risk. If he were to have an episode of hypoglycemia while working, no co-worker would be able to do even the simplest things, such as giving him candy or a glass of juice. Further, supervisors may assign him to work inappropriate time sequences, not realizing the importance to the person of regular hours and break times. Finally, if discovered to have diabetes, the employee is often fired without regard

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to his performance on the job to that time or the fact that he had less absenteeism resulting from medical problems than any of the other co-workers. Even when there is job security, upward or lateral mobility may be limited.

Finally, the desire to be financially independent by working may be so great as to induce the person with diabetes to ignore his care, thereby increasing the chance of complications. The physican can almost never modify his patients' attitude in this circumstance.

f. The Cost of Being a Diabetic Patient

More than anything else, the concern of persons with diabetes and their families is that the disease will place excessive demands on their financial resources. Indeed, it is expensive to have diabetes. Besides the cost of medication and physician visits, the additional expense of possible hospitalization is a major concern.

This must be considered realistically in light of limited job oppurtunities and less than adequate health insurance. It is people with fixed and limited incomes who are most affected by the "routine" cost of care. In very low income failies, even the addition of financial aid and food stamps may not be enough to supply the essentials necessary for diabetic control and the necessities of life.

g. Military Service

The armed forces through the years have uniformly discriminated against people with diabetes both by denying the opportunity serve and limiting advancement if diabetes is discovered while in the service. The presence of diabetes mellitus precludes appointment to the military academies.

This rejection adds to the sense of inadequacy which the person frequently feels as a result of having diabetes. For many economically deprived in our society, serving in the military offers the only opportunity for training and upward mobility. It is clear that in peace time most jobs in the military are non-combatant. It would seem that people with diabetes as well as non-diabetic individuals could fill these positions. As expressed in the workshops of this workgroup, many young people with diabetes would willingly serve in alternative service if offered. Perhaps this would allow those persons to obtain subsequent educational and medical benefits.

h. Health and Life Insurance for People with Diabetes

While information regarding the health and life insurance problem is being considered by other study sections of the commission, it should be reemphasized that obtaining such insurance is a constant

source of frustration encountered by all people with diabetes. When insurance is available to persons with diabetes, it is expensive and far less than adequate. In addition, little incentive is present in these policies to encourage preventive care in an effort to minimize complications and reduce future health care costs.

i. Society and the Diabetic Patient

The public in general has very little accurate information regarding diabetes. Diabetes is often considered in the same category as epilepsy and mental illness. Many people with diabetes, as a result of these prevailing attitudes, try to hide their illness from other members of society. This sets the stage for society to react in an inappropriate way to the individual with diabetes.

Examples of inappropriate reactions of society include discimination when applying for a driver's license, which sometimes requires visits at six-month intervals to the physician and hours of bureaucratic red tape in renewal. Ignorance of diabetes in law enforcement agencies results in numerous "drug busts" of teenagers caught with diabetic syringes and insulin. More distressing is the fact that even with proper identification many young people with diabetes still go through the humiliation of arrest. All too frequently police mistake hypoglycemia for alcohol or drug intoxication, often with disastrous results. All physicians treating diabetic patients relate other experiences equally as devastating.

j. Emotional Impact of the Health Care System on the Diabetic Patient

1) Fee-For-Service (Private Medical Care System): The Majority of persons with diabetes receive medical care from private, fee-for-service physicians. Both diabetic patients and their families express dissatisfaction at times with the quality of this care. Numerous causes for this dissatisfaction exist. Doctors frequently do not spend enough time explaining the nature of the disease or in educating the patient in self-management techniques. There seldom are trained paramedical personnel to assist with this training in the office setting. Often the doctor himself is not aware of all the details of the complex management of diabetes. Indeed, many patients have no access to information regarding qualifications of their doctor to treat diabetes. Doctors often unnecessarily scare patients by a recitation of all the myriad complications which may accompany diabetes while not being able to tell the patient how to avoid them.

2) Clinics and Public Health Facilities: Many patients have their diabetes treated in settings other than the private physician's office. These patients may include the urban and rural poor and those diabetic patients who are in prison, on

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Indian reservations, or in the military, all of whom depend on public health clinics for their ongoing care. The problems encountered in the private health care system are greatly magnified and other more significant problems are found as well. First, patients who are served by this type of facility, as a group, tend to have less education and less sophistication to understand medical processes. This means that self-management of their disease will invariably be more difficult. In this setting, health education for a patient clearly becomes more difficult. There are frequently additional environmental, cultural, and even language barriers to surmount. Often the goals of the educational process must be adjusted to fit the social environment without regard to achieving maximal care.

Far too often standards set by the physician or health care team in this social setting are unrealistic. The patient becomes discouraged, omits clinic visits, and falls far short of the reasonably good control he might be able to achieve had reasonable expectations been set.

The medically indigent patient who fails to show up for his appointments frequently elicits the response that he is too lazy, too drunk, or too busy shooting heroin to bother to save his own life; and little or no attempt is made to contact him to follow up these broken visits. Patients in this setting frequently miss appointments, but there may be a variety of reasons unknown to the doctor. The patient may not have understood prior instructions. If he arrives on the wrong day or misses his appointments, there usually is no one to help with rescheduling. He may see no reason to continue to come to the clinic if he is having no symptoms. He may lack the cost of transportation to the clinic.

Continuity of care is another area in which clinic patients are at a disadvantage. Many teaching facilities rotate their medical personnel through different treatment areas at frequent intervals. On consecutive visits a patient may see different doctors and have to tell his story many different times. From each doctor, he hears different and often conflicting sets of advice. Though this advice may vary in what appears to the doctors to be only minor ways, the patient has no way of determining which variables are important. He may conclude that the doctors are incompetent, or that his condition is worsening, or that no one really cares. Moreover, the patient never has the opportunity to establish an ongoing and trusting relationship with a single doctor.

This lack of continuity is also an impediment for the doctor. Given a diabetic patient in poor control, he is frequently unable to judge whether the problem is lack of

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compliance, lack of understanding, or a refractory medical
problem. Although there have been major improvements in many
hospital clinics during the last few years, especially with the
incorporation of nurse practitioners and physician assistants,
medical care in this setting continues to be poor. More unfor-
tunately, the number of indigent patients grows each year and
staff and facilities are unable to keep pace.

3) Prepaid Health Facilities: These facilities offer ele-
ments of both public and private health care systems. It is be-
yond the scope of this report to indicate the degree of success or
failure they have had in the past. However, a prepaid diabetes
health care program would seem to offer many advantages, i.e.,
adequate incentives for preventive care and a medical unit respon-
sive to the scope of the problem. At the present time, there is no
health maintenance organization (HMO) with its emphasis on dia-
betes.

4) Emergency Services: Persons with diabetes frequently
need access to immediate medical care when the primary physician
is unavailable or the clinic not open. Difficulty frequently is
encountered identifying adequate emergency services. Most dia-
betics will recognize problems with their diabetes more clearly
than the doctor they will meet in an emergency room. Knowledge
that this is so may be frightening even before entering the
treatment facility. Add to this long waits and impersonal atti-
tudes, and it is small wonder that emotions are aroused in
emergency facilities; and, of course, as a result the control of
diabetes worsens.

Frequently, important points of management such as prompt
treatment of infection are ignored by the staff. In a true
emergency, such as ketoacidosis or hypoglycemia, the emergency
room treatment may again fall short; and it is not uncommon for
relatives to feel the necessity to argue the point with the
staff that the patient has hypoglycemia and should be treated.
Diabetic coma, a clear medical emergency, requires prompt
therapy from experienced clinicians for the best chance of
survival.

In many emergency facilities, many hours may elapse before
adequate care is initiated.

Despite these problems, there has been increasing use of
emergency facilities as primary care centers in the past few
years. It is not evident that education regarding diabetic
care has correspondingly increased among the staff of these
facilities.

5) <u>Information and Education for the Diabetic Patient</u>:
Most diabetic patients stress the importance of having a single
source of information to which they can turn when they have
medical or social questions about diabetes.

Most states have a wide variety of programs designed to
help persons with diabetes through counseling, education,
rehabilitation, and other social services. The problem faced by
diabetic patients is that with few exceptions there is no readily
available source to which they can turn for information about
the availability and nature of such programs. When available,
the information frequently is conflicting or incomplete. Most of
the time the acquisition of such information is so time consuming
as to be essentially unavailable, and many patients feel that the
health care provider has no better knowledge of the resources
available than he does. An indication of the serious desire for
information is seen in Wisconsin where just a few months after
implementing a diabetes information telephone line they were
receiving several thousand calls per month. Similar systems
clearly would be of benefit in other states.

Educational material, though available in most treatment
facilities, is often inappropriate. It may be incomplete or
beyond comprehension to the patient or the family; or it may
contradict what the physician has told the patient. These problems
will be emphasized by other sections of the commission report.

4. SPECIAL SOCIAL PROBLEMS OF SUB-POPULATIONS

While most problems of psychosocial adjustment are common to all
persons with diabetes, many people, by virtue of belonging to special sub-
populations, have unique problems. These persons invariably have some
of the most intense psychosocial problems adversely affecting the course
and outcome of their illness. In general, these groups can be charac-
terized by being at some disadvantage, such as by age, location, or
ethnic background. There are easily 50 or more such groups which could
be cited in this report; however, space limitations preclude mentioning
all but a selected few.

a. American Indians with Diabetes

American Indians are a special group for consideration because of
their high rate of diabetes. For example, among the Pima Indians nearly
half the population over age 35 has diabetes. In addition, American
Indians live in some of the worst poverty situations known in the
United States, and, therefore, are subject to the effects of substandard
care common to the poverty-ridden everywhere. The common diabetes-
related problems are responsible for nearly 20% of hospital admissions.

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The disease is so widespread among the Pimas that it is part of their life; and the complications of diabetes are accepted as part of the natural course of advancing age.

Although overall medical care has greatly improved as a result of the Indian Health Service, full health care, including diabetes care, has been slow to be implemented. This is true in part because of the persistance of tribal customs, folk medicine, and, frequently, unacceptable medical facilities.

b. The Elderly Person with Diabetes

The elderly person with diabetes has unique problems primarily involving social isolation, decreased financial independence, and progressive physical impairment.

As a person ages, the family, so important as a support mechanism for all diabetic patients, begins to disintegrate; spouses, friends, and children die, move away, or ignore the plight of the aging diabetic person.

There are decreased financial resources because most elderly people today have little more than retirement or social security money available. Even the smallest medical expense may overburden limited incomes. Loss of health insurance may necessitate switching to treatment facilities which are less adequate but will accept payment from government supported insurance, e.g., Medicare-Medicaid.

Finally, increasing physical disability secondary to decreased vision, cardiovascular disease, cerebrovascular disease, or the complications of diabetes decrease both mobility and motivation. All of these factors make psychologic adjustment to aging difficult. It is not infrequent to observe prolonged depression, paranoia, or withdrawal phenomena complicating attempts at treatment.

At the end of the line is confinement to a nursing home. Here the person with diabetes finds personnel ill-trained to manage the myriad of problems associated with his physical and emotional state. Poor medical care and inadequate supportive services are common. In most cases the health care systems in the nursing homes runs parallel to, and independent of, the mainstream of medicine. There have been few attempts to find or develop ways to monitor diabetes care in nursing homes. These patients do not complain because they cannot.

c. People with Diabetes in Prison

It is difficult to determine the exact number of persons in prisons, since absolutely no data are available indicating the number of prisoners with diabetes.

The available estimates of the prison population are in the range of 300 to 400 hundred thousand people. Assuming there is a 5% incidence, then at least 15- 20,000 people with diabetes are presently incarcerated. The diabetic prisoner is in a difficult position for self-managing his disease. Guards and administrative personnel have no special training in the problems of the prisoner who has diabetes and may consider him to be a troublemaker or malingerer. Indeed, some diabetic prisoners try to purposely manipulate their therapy to avoid the rigors of prison life. This, of course, may at times significantly contribute to the development of diabetic complications. It is not uncommon for diabetic prisoners to refuse their insulin in order to induce ketoacidosis and their removal from undesirable detention facilities.

d.   The Rural Person with Diabetes

Three central problems face the rural diabetic. The first is the relative scarcity of trained medical personnel in rural areas (the doctor-patient ratio is less than half that of cities). The second is very low population density which results in longer travel time to medical facilities. And third is the application in rural settings of classic self-management techniques used in urban areas.

The type of medical service available in rural areas is substantially different from those in urban areas. Most physicians are in a general practice situation. The rural doctor, far from medical centers and overworked, finds it difficult to set up specific diabetic care programs or initiate diabetes education.

Often the rural diabetic patient is sent to a distant regional medical center for initial diagnosis treatment and education then returned home to the care of the general physician. Long distances make routine visits less frequent. Often the visits are only for major problems. Emergency transportation and ambulance services may or may not be available. Lastly, the urban self-management program based on "normal" eating times and urine checks may not be normal in the rural setting where time of meals is dependent on work schedules in the field.

e.   The Parent with Diabetes

Rarely does the evolving family have available premarital or pre-pregnancy counseling. Family planning is a difficult subject to discuss with young people who have diabetes because of the strong emotional feelings related to "bringing another diabetic into the world." The ambivalence of both wanting and not wanting a child is frequently a source of marital discord. It is at times such as these that adequate psychological and medical advice is needed, but it is frequently unavailable or inappropriate.

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Although most pregnant women are normally concerned about the wel-
fare of the baby, a pregnant diabetic must not only worry about the preg-
nancy itself, but both the effect of her own diabetes on the developing
fetus and the possible worsening of her own disease because of the preg-
nancy. Clearly, these months are a period of severe stress for the mother
and family.

The financial burden may add even more to the emotional strain.
The cost of pregnancy for the diabetic patient is likely to be
high because far more prenatal care is necessary if the pregnancy
is to have the best possible chance. This can include frequent
hospitalization and even spending the last several months of
pregnancy in the hospital.

f.   The Adolescent with Diabetes

There is little doubt that diabetic adolescents run a greater risk
of developing emotional problems than their nondiabetic counterparts.
The influence of these emotional factors on the management of the disease
is evident to any practicing diabetologist but, unfortunately, there has
been little research into the psychodynamics of the family or individual
which might be of value in reducing this risk.

The teen years are a time of turmoil and emotional upset in most
youngsters, not only those with diabetes. It is critical, therefore, for
the physician to recognize this transitional period and its normal pat-
terns. He should be aware that adolescence is a time of rapid growth from
dependence to independence; that the adolescent wishes to test the rules
he has faithfully followed as a child; that this often leads to experi-
mentation in many phases of life; and that diabetes is not immune to this
testing. A common clinical expression of this testing is experimentations
with insulin dose and its attendant complications. Another is a desire to
avoid parental interference in the disease by revolting against the dia-
betic diet. The emotional instability of adolescence is further
aggravated by the burdensome details of self-treatment which are imposed
by the disease, by parental insistence, or by physician insensitivity.

There is a common progression through which many pass during their
adolescence. The developing adolescent, at first, accepts the diagnosis
while hoping for a cure, or at least remission. After several years of
not achieving this goal, and with the realization of the frequent compli-
cations, he finally denies the actual existence of the disease. What
emerges in the adolescent is a denial reaction which most would call
"self-destructive behavior."

At this point, many physicians become so frustrated with the
adolescent and his behavior pattern that they frequently give up, thereby
allowing poorer and poorer control. By giving less and less time to the

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adoloscent, the physician ultimately forces the young diabetic patient to search for more sympathetic medical care. At this time of greatest need, the diabetic adolescent is often abandoned, and, in some cases, physician trust is never established again.

Adolescents with diabetes often also have particular problems with their parents who see the ravages of the poor control of diabetes and frequently respond by trying to enforce standards of control on the adolescent which are not only psychologically inappropriate, but medically inappropriate as well. One area of difficulty is urine testing, which can rapidly become an area of dissension, especially if parents attach moral judgments to the results.

Society also reacts poorly to the adolescent with diabetes. In this age of drug abuse, the possession even of an insulin syringe may result in arrest. In some areas a diabetic youth can be expected to be picked up by the police several times a year for this "offense."

These problems can, and do, develop into serious lifelong psychological disabilities. Depression and suicide are more common in the adolescent with diabetes. Manipulation of control may continue to be used in later years as a device to gain attention.

Despite all these problems most teenagers progress to adulthood, but it is difficult to assess the medical and emotional scars left by the experience of those adolescent years.

5. <u>RECOMMENDATIONS TO LESSEN THE PSYCHOSOCIAL IMPACT OF DIABETES</u>

In making these recommendations for attenuating the psychosocial impact of diabetes, the workgroup recognizes that the disease diabetes and the social interactions of a person with diabetes are not isolated from the rest of the society. Unless contiguous social problems are addressed and an effective total health care system designed, no change will occur.

It is also hoped that the following recommendations will not be left to stand alone but that they will be complementary to and incorporated into all reports submitted to the Committee on Scope and Impact.

Based on the information presented, we find the following to be almost universal psychosocial problems among all diabetics, their families, and society, and we offer some recommendations to lessen their impact.

a. Most persons with diabetes are aware of their diffuse emotional involvement with their illness, but they cannot identify sources of psychological counseling for themselves or their families. This

represents a major impediment to the person with diabetes in helping him-
self manage his illness. Further, it is apparent to the workgroup
that most health care providers are unaware of the major importance of the
psychosocial situation which influences the treatment and outcome of per-
sons with diabetes.

RECOMMENDATION 1:

Recognizing that psychological factors play an important role in
the total well-being of many persons with diabetes, it is strongly
recommended that:

> Specific funding be set aside in all new diabetes cen-
> ters for continuing research into the problem of psy-
> chological influences in the diabetic state as it
> relates to morbid events;

> Newly funded diabetes centers be funded so as to in-
> corporate adequate psychological counseling services
> to all populations and age groups they serve;

> That the juvenile with diabetes be considered an
> exceptional case where psychological counseling is
> not only helpful but mandatory if reasonable psycho-
> logic and medical outcome is to be expected;

> That the maintenance of a well-functioning family be
> considered of the utmost importance in any age group
> to improve the outcome of its members with diabetes
> mellitus. To achieve this end, counseling must be
> available and appropriate for the entire family.

PROJECTS:

1) Identification of specific factors in the family unit
   which would allow detection of those diabetic patients
   who may develop psychological blocks to self-management.

2) Further evaluation of the psychologic outcome of psycho-
   logical stress in persons with diabetes mellitus and how
   the effect can be modified to improve outcome.

3) Determination of the extent of psychological and psy-
   chiatric intervention necessary to reduce the level of
   self-destructive behavior by the diabetic patient during
   the formative years.

4) Exploration of behavior modification and biofeedback in

modifying self-management techniques.

5) Development of educational modules for stressing the psy-
chosocial impact of diabetes on the patient and the incor-
poration of the modules in health care professional train-
ing programs.

6) Development of training programs in counseling for nurses,
physician assistants, and social workers to increase the
psychological interface between health care professionals
and the diabetic patient and his family.

b. The health care team, families, and the patients themselves
must have access to information regarding all aspects of diabetic care,
counseling, rehabilitation, and research if they are expected to cope with
the illness.

RECOMMENDATION 2:

We, therefore, strongly support the concept of a
National Diabetes Advisory Council. It is hoped that
this advisory body would provide current information
regarding all aspects of diabetic care, counseling,
rehabilitation, and research to the general public, to
health care providers, and to all persons with dia-
betes.

The existence of the advisory board could also be the
stimulus for existing governmental and private agencies
to compile and disseminate resources currently avail-
able for the care and rehabilitation of persons with
diabetes.

PROJECTS:

1) Establish a nationwide "hot-line" system which would allow
all interested persons to receive accurate current infor-
mation regarding all aspects of diabetes.

2) Development of reference sources for each geographic region
identifying all existing treatment facilities and social
agencies involved with the disease.

c. Among many health care providers there is the lack of uniform
understanding of both the treatment and natural history of diabetes. When
this is transmitted to the patient and family it leads to feelings of un-
certainty and frustration and sets the stage for poorer self-management.

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RECOMMENDATION 3:

> That increased support be given to the training of
> health care providers to better understand the disease
> diabetes, and its extremely multifaceted complications and
> treatment, thereby lessening the uncertainty and im-
> proving the relationship between provider and patient.

PROJECTS:

1) Exploration of the extent to which diabetes is being taught
   to health care providers in training programs.

2) Development of educational modules for these training pro-
   grams to fully acquaint the trainee with the natural history
   of diabetes and the best therapeutic approach to the disease.

3) The support of "elective time" training for medical students
   and other health care professionals in diabetes centers.

d. Persons with diabetes have major psychosocial problems dealing
with an uninformed public at all levels, leading to generally poorer manage-
ment of their diabetes and significantly more morbid events.

RECOMMENDATION 4:

> We strongly support a national public education pro-
> gram aimed at identifying diabetes as a significant
> health problem in the United States. The identifi-
> cation of diabetes with other diseases like hyper-
> tension or heart disease, hopefully, would decrease
> inappropriate societal reaction to the person with
> diabetes.

e. Job discrimination directed at persons with diabetes is almost
universal and represents a significant social barrier to self-actualiza-
tion. Job discrimination seems to occur at all levels of employment in
both the private and governmental sectors.

RECOMMENDATION 5:

> That the public information program outlined in previ-
> ous recommendations be directed at employers through-
> out the country so as to lessen the impact of diabetes
> on employees and discourage job discrimination. It is
> recognized that as long as employers are penalized for
> hiring diabetics, e.g., by increased insurance premi-
> ums, discrimination will continue.

It is further strongly recommended that the Armed
Forces reconsider its position regarding induction of
persons with diabetes. If not actually incorporating
these persons into the military, the federal govern-
ment should encourage and support alternate service
with full benefits.

f.   While problems of living occur at all ages, special psycho-
social problems are created or intensified for many persons with diabetes
by virtue of the specific age group to which they belong.

Persons with diabetes living in certain economic or ethnic
communities need unique programs of diabetic health care delivery to
lessen the psychosocial impact of the illness.

RECOMMENDATION 6:

It is strongly recommended that in the planning of
diabetes centers, whether they be treatment or re-
search centers, careful attention be given to both
the psychological and medical needs of frequently
forgotten sub-populations, and, wherever possible,
additional suitable programs be initiated to help
these groups cope with diabetes. These may include
such target groups as (list by necessity incomplete):

1.   Adolescents
2.   Parents of diabetic children
3.   Young adults and the evolving
     family
4.   Elderly
5.   Rural Americans
6.   Migrant Farm Workers
7.   American Indian
8.   Non-English speaking communities
9.   Diabetic patients in prisons
10. Under-serviced communities in
     all areas

As a corollary of this recommendation, it was felt by
the entire workgroup that funded diabetes centers
should not limit their activities to the physical
bounds of the center, but, rather, initiate outreach
programs into both urban and rural under-serviced areas.
These programs may provide, as a minimum, reasonable in-
formation and education services even if they are unable to
completely treat these populations.

Further, it is recommended that these funded centers encourage the expansion of existing diabetes facilities, e.g., diabetic camps, educational centers to include all age groups, families, and specifically under-serviced populations in year-round education and counseling.

PROJECTS:

1) Assessment of the extent of medical and psychological service currently available to targeted diabetic sub-populations.

2) Establishment of model care and counseling programs uniquely designed for targeted groups.

3) Training in diabetes of community health workers from the target population to assist the health care providers in dealing with the full scope of the disease.

The implementation of this recommendation may best be accomplished by the consortium concept of diabetes centers. It must be emphasized that health care delivery systems, education, or counseling programs implemented without members of these specific target populations actively assisting in the planning will be far less likely to be successful.

g. At the present time, there are many persons with diabetes who have limited health care only because they are unable to identify acceptable, adequate, and accessible treatment facilities. This is a daily concern to these persons.

RECOMMENDATION 7:

While it is recognized that extensive research into the cause of diabetes is needed in order to find a cure, those persons who presently have diabetes, or who will be diagnosed in the immediate future, must have access to reasonable health care. Therefore, it is recommended that the funded diabetes centers be models of comprehensive care so as to include medical, social, and psychological support systems.

PROJECT:

To support the concept of a categorical health maintenance organization (HMO) system organized to promote comprehensive health care to a specific targeted diabetic population.

h. While most communities have available and accessible emergency services, physicians staffing these services frequently lack sufficient knowledge regarding care of the diabetic patient.

RECOMMENDATION 8:

Diabetes centers should assess the quality of care now being provided for targeted diabetic populations in the emergency setting. These centers should further be directed to reach out via professional education to improve the quality of care provided in these facilities.

PROJECT:

1) Assessment of the extent and appropriateness of existing emergency diabetes services for specifically targeted diabetic populations.

2) Development of educational modules in the treatment of diabetes to be included in emergency medicine training programs.

i. Present and future health care costs are a constant source of frustration for each person with diabetes. Besides the inability to pay for today's care, the presence of diabetes may severely limit earning power and ultimately lead to decreased ability to pay for care in the future. In addition, when financial resources are limited, health care will invariably be sacrificed as being of lesser importance than other primary needs.

It is beyond the scope of this report to determine the extent of coverage of health care costs for the diabetic patient in the future. We recognize that even complete coverage of all medical costs for all diabetic patients will not guarantee adequate facilities or sufficient health care providers. It is important to recognize the constant psychological burden placed on the diabetic patient and the family by the cost of the diabetes.

Clearly, in juvenile onset diabetes the extent and cost of medical services needed during the lifetime of the individual is so enormous as to cause serious doubts that full attainment of adequate medical services ever occurs.

RECOMMENDATION 9:

That those young people with diabetes who will live with diabetes for a lifetime be considered in the

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category of having a catastrophic illness in any
Federal health legislation enacted in the future.

j. At present, there is no uniform definition of diabetic-related disability by local and federal governmental agencies. As a result, persons with diabetes are largely unaware of their rightful entitlement to economic and social aid as a result of their illness.

RECOMMENDATION 10:

That under the direction of the National Diabetes
Advisory Council existing federal and local agencies
clearly establish guidelines for disability in dia-
betes. These guidelines, together with available re-
habilitation resources, should be disseminated to
both health care providers and patients throughout
the country.

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IX. Report of the

WORKGROUP ON

ECONOMIC IMPACT

of the

COMMITTEE ON SCOPE AND IMPACT

to the

National Commission on Diabetes

Chairman:

Paul S. Entmacher, M.D.

IX. REPORT OF THE
WORKGROUP ON ECONOMIC IMPACT

A. SUMMARY

It is estimated that in 1975 the overall cost to the nation
resulting from diabetes will be $5.34 billion. This is divided into
indirect costs, which result from loss of productivity due to morbidity
and mortality, and direct costs, which reflect expenditures for
medical and related services. The direct costs attributable to
complications of the disease have been estimated to be $297 million.
The indirect costs due to complications cannot be measured because of
lack of adequate data. If the costs resulting from complications are
included, the total economic cost approaches $6 billion.

B. STATEMENT OF THE PROBLEM

It is extremely difficult to estimate the full economic impact of
diabetes, and the data that follow must be considered as significantly
underestimating the situation. Because of the nature of the disease,
many of the complications, such as blindness and vascular disease,
may lead to disability (and, in the case of vascular disease, to death),
and the complication will be listed as causative with no reference to
diabetes. Also, the impact that diabetes has as a contributing factor
leading to disability or death from unrelated diseases cannot be
measured.

The growth in demand for governmental services, coupled with
severe budgetary constraints, has led to increased usage of benefit-
cost analysis as a guideline for allocating public funds. While
private investment decisions are motivated by profit, public invest-
ment decisions must attempt to select those projects which yield the
greatest net social benefits, and the cost of alleviating one disease
must be compared with similar costs for other diseases. The likelihood
of achieving eradication of a disease must also be taken into
consideration.

C. IMPACT OF THE PROBLEM

In aggregate, the total economic cost in 1975 due to diabetes
will be $5.34 billion. This does not include the cost attributable
to complications of the disease.

D.   STATE OF THE ART

1.   INTRODUCTION

In the area of disease control, one way of defining the potential benefits of public investments is to assess the costs a disease imposes upon society and to project this amount as the potential cost-benefit which would be derived from alleviating or eradicating the disease.   The costs of a disease are defined as: (1) medical care expenditures for treatment, detection, and prevention; (2) losses in productivity; and (3) the physical and psychological discomforts associated with an illness.   Much research in the area of public investment and the economic benefits and costs of disease control has been done in the past (1, 2, 3, 4).   This report follows the basic methodology described by the National Heart and Lung Institute Task Force on Arteriosclerosis (5), its task force on Respiratory Diseases (6), and Dorothy Rice's Estimating the Cost of Illness (7).

In this report, we deal with only half of a complete benefit-cost analysis, the economic costs of diabetes.   The report of the Socio-economic Workgroup, which precedes this report, focuses on the social and psychological impact of diabetes.   The costs we are concerned with here represent the potential economic benefits which could be obtained by eliminating the disease.   The efficacy (using economic criteria) of public investment designed to achieve this end requires information beyond the cost of diabetes, but it is important, first, to know the size of the investment needed to eliminate diabetes.   The cost of diabetes minus the cost of the program to eliminate diabetes gives us the expected net benefits which could be obtained from investments in alternative projects.   However, in our economic projections, if the objective of public investments is to achieve the highest rate of return, one cannot determine whether or not a single project should be implemented without looking at the rate of return for alternative projects.

2.   OVERVIEW

In the following discussion, an estimate of the direct costs, as well as the indirect costs, will be made.   In addition, an attempt will be made to measure the impact of complications of the disease. This will be included in a separate section.   A series of End Notes will follow the text and these will be referred to during the discussion.   Appendix A outlines estimation procedures.   Appendix B presents a series of background tables used for development of data presented in the text.

The total economic cost of a disease is arrived at by combining the following:

Indirect Costs

This is defined as the loss in current productivity and earnings attributable to diabetes. These productivity and earning losses are a result of diabetic morbidity and mortality (End note 1) among employed diabetics, diabetic women keeping house, and totally disabled diabetics.

Direct Costs

These costs have taken into account expenditures for prevention, detection, treatment, rehabilitation, research, training, and capital investment in medical facilities. In terms of types of services or object of medical expenditure, direct costs include amounts spent for hospital and nursing home care, physicians' and other medical professional services, drugs, medical supplies, research, training, and other non-personal services.

The cost estimates provided in this report are projections for 1975. Data limitations and resource constraints have made it impossible to include all possible cost components. The direct cost estimates do not include the costs for construction of medical facilities and research related to diabetes. The indirect costs have excluded the impact of psychic costs suffered by diabetics. These exclusions, along with the difficulty in estimating the impact of complications of the disease, result in a minimum estimate of the total cost of diabetes, though our estimates do point up the magnitude of the various costs diabetes imposes upon society.

a. Indirect Costs

As defined previously, the indirect cost of diabetes is the loss in current productivity and earnings attributable to diabetes. According to our estimates, the United States will lose $1.76 billion in earnings in 1975 because of diabetes. Stated another way, 164,000 productive years will be destroyed by the disease in 1975.

As indicated previously, indirect costs such as psychic cost resulting from the physical discomfort, changes in life style, and increased uncertainty suffered by diabetic patients are not included here. These intangible costs, although a significant cost aspect of diabetes, would be extremely difficult to quantify in monetary terms.

Before the indirect cost of diabetes can be calculated, the gross U.S. population (Table 11) must be adjusted according to the labor force participation rates by age and sex (Table 13). The labor force participation rate is the proportion of a population employed or seeking employment; from this the expected number of diabetics in the labor force may be computed (End note 2). Given the number of diabetics in the labor force, and a full employment rate of 96% (End note 3), we can now estimate the number of employed male and female diabetics by applying the above rates to the diabetic population. These figures are shown in Table 1. The total number of diagnosed and undiagnosed diabetics was derived from the prevalence rates by age and sex in the U.S. (Table 12).

Of the 6.23 million persons with diabetes (estimate) in the United States, about 45% are expected to be employed. For diabetic males, 65% are employed, as compared to 31% of the diabetic females. For the nation as a whole, given our 4% unemployment rate, approximately 74% of the males and 40% of the females would be expected to be employed. The relatively low employment ratios among diabetics may reflect the greater prevalence of diabetes in the older and female segments of the population, although these segments, in general, have comparatively low labor force participation rates. The prevalence of diabetes among older and female members of the population tends to reduce the proportion of the economic cost of diabetes in terms of productivity losses as compared with other diseases which more frequently affect younger people.

1) Morbidity Among Employed Diabetics: Earning losses attributable to morbidity among employed diabetics are equal to work-years lost (work-days lost per employed diabetic per annum, as shown in Table 13, times the number of diabetics divided by 250) times the expected earnings (Table 15) by age-sex cohorts. These figures are shown in Table 2. The estimated work-years (productivity) and earnings lost for employed diabetics are 31,507 and $397,747,000 respectively. Of these totals, employed males account for approximately 80% of the earnings lost and 67% of the work-years lost. Although employed female diabetics account for 42% of the total number of employed diabetics, their relatively lower expected earnings reduce their share of total earnings lost to about 20%.

2) Mortality Among Employed Diabetics:

a) Annual: Estimated work-years and earnings lost due to mortality among employed diabetics in 1975 are 5,289 and $63,415,000 respectively. Work-years lost are equal to one-half the

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Table 1

Number and percentage distribution of productive* diabetics (diagnosed and
undiagnosed) by age, sex and employment status in the United States

(Estimated 1975)

| Age Group | United States | | | |
	Employed Male	Employed Female	Housewives	Total
16-24	93,695	110,274	36,839	240,808
25-44	264,341	231,047	124,685	620,073
45-54	618,826	412,164	223,981	1,254,971
55-64	427,557	276,417	226,950	930,924
65-74	167,422	142,495	494,647	804,564
Over 75	34,885	32,346	375,943	443,174
All Ages	1,606,056	1,204,743	1,483,957	4,294,514

Percentage Distribution

Age Group	Employed Male	Employed Female	Housewives	Total
16-24	5.7	9.1	2.4	5.5
25-44	16.4	19.1	8.3	14.4
45-54	38.4	34.2	15.0	29.2
55-64	26.5	22.9	15.2	21.6
65-74	10.3	11.7	33.3	18.7
Over 75	2.1	2.6	25.2	10.3
All Ages	100.0	100.0	100.0	100.0

Note: Tables: 1, 2, 3 and 4 In Appendix B.

*Unemployed males and females excluded.

Table 2

Work-years and earnings loss due to diabetic morbidity in the United States
by age, sex, employment status and percentage distribution

(Estimated 1975)

Age Group	Employed Male		Employed Female		Total	
	Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)
16-24	862	$ 6,048	926	$ 4,938	1,788	$ 10,986
25-44	2,431	35,215	1,940	15,838	4,371	51,053
45-54	8,416	135,876	3,462	27,941	11,878	163,817
55-64	5,814	86,523	2,100	17,045	7,914	103,568
65-74	3,348	45,067	1,082	7,659	4,430	52,726
Over 75	725	9,759	401	2,838	1,126	12,597
All Ages	21,596	318,488	9,911	79,259	31,507	349,747
	Percentage Distribution					
16-24	3.9	1.8	9.3	6.2	5.6	2.5
25-44	11.2	11.0	19.5	19.9	13.8	12.9
45-54	38.9	42.4	34.9	35.2	37.6	41.3
55-64	26.9	27.0	21.1	21.5	25.1	26.1
65-74	15.5	14.1	10.9	9.6	14.0	13.1
Over 75	3.3	2.8	4.0	3.5	3.5	3.0
All Ages	100.0	100.0	100.0	100.0	100.0	100.0

Note: Derived from Tables 3 and 5 in Appendix B.

number of deaths (Table 16), based on the assumption that there is
an equal probability of dying on any day of the year. Therefore,
the average time lost due to death in a particular year is equal to
the median or 182.5 days lost per death. Mortality losses for em-
ployed diabetics are shown in Table 3. The seemingly small number
of deaths among employed diabetics can be explained by two factors.
First, employed diabetics probably have less severe diabetes than the
general diabetic population. Second, death among diabetics in general
is frequently attributed to causes other than diabetes.

b) <u>Present Value of Lifetime Earnings</u>: The indirect
economic cost of mortality for diabetes to the nation as measured in
terms of the discounted present value of lifetime earnings of persons
who will die in 1975 is $1.066 billion. This figure was obtained by
multiplying the estimated number of deaths from diabetes by age and
sex which will occur in 1975 (End note 4) by the expected value of
future earnings. Future earnings were discounted at 4% to take into
account interest that could be earned in the interim with an adjustment
made for increased productivity. The estimated present value of
lifetime earnings by age and sex is shown in Table 17. Comparable
figures based on earnings discounted at 6% are shown in Table 18.
The earnings figures were computed from discounted earnings made
available for 1972 from Barbara Cooper of the Social Security Ad-
ministration (8) (Table 19), and adjusted by the Metropolitan Life
Insurance Company (9) based on the current trend of mean income.

The estimated number of deaths from diabetes in 1975
is shown in Table 4. Also shown in this table are the indirect costs
by age and sex which were derived by multiplying the number of deaths
by the discounted earnings shown in Table 17. The total indirect costs
due to mortality were $1.066 billion, with approximately $683 million
due to mortality among males and $382 million due to female mortality.

3) <u>Household Production</u>: Not all productive activity
takes place in formal exchange markets where wages and salaries are
explicitly paid. A large portion of the productive activity in this
country is performed by women keeping house who receive no direct
monetary remuneration. To exclude the productive activities in the
household would result in a gross understatement of the indirect cost.

Although a number of approaches have been used to impute
a value to housewives' services, here the market cost approach as
defined by Wendyce H. Brody from the Social Security Administration in
a paper, "Economic Value of a Housewife" (10), is adopted (End note 5).
This approach is based on a time and motion study which takes into
account the variations in the housewife's production function by age

Table 3

Annual work-years and earnings loss due to diabetic mortality among employed diabetics by age, sex and percentage distribution in the United States

(Estimated 1975)

Age Group	Employed Male		Employed Female		Total	
	Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)
16-24	29.5	$ 150	21.5	$ 114	51.0	$ 264
25-44	396.8	5,748	171.6	1,400	568.4	7,148
45-54	618.0	9,977	338.9	2,735	956.9	12,712
55-64	1128.3	16,791	681.1	5,528	1809.4	22,319
65-74	800.3	10,768	476.0	3,369	1276.3	14,137
Over 75	375.9	5,059	251.0	1,776	626.9	6,835
All Ages	3349.2	48,493	1940.0	14,922	5289.2	63,415

Percentage Distribution

Age Group	Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)
16-24	.8	.3	1.0	.7	.9	.4
25-44	11.8	11.8	8.8	9.3	10.7	11.2
45-54	18.4	20.5	17.4	18.3	18.0	20.0
55-64	33.6	34.6	35.1	37.0	34.2	35.1
65-74	23.8	22.2	24.5	22.5	24.1	22.2
Over 75	11.1	10.4	12.9	11.9	11.8	10.7
All Ages	100.0	100.0	100.0	100.0	100.0	100.0

Note: Derived from Tables 5 and 6 Appendix B.

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Table 4

Estimated number of deaths and indirect costs due to diabetes, United
States, 1975

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	37,000	15,175	21,825	1,065,573	683,351	382,222
Under 1	16	11	5	1,499	1,173	326
1-4	14	9	5	1,412	1,056	356
5-9	21	8	13	2,274	1,145	1,129
10-14	51	19	32	6,700	3,314	3,386
15-19	64	32	32	10,644	6,659	3,985
20-24	122	62	60	22,652	14,635	8,017
25-29	235	138	97	46,530	34,013	12,517
30-34	310	166	144	56,625	39,596	17,029
35-39	414	239	175	70,889	52,309	18,580
40-44	597	320	277	86,770	61,113	25,657
45-49	1,013	516	497	119,669	81,229	38,440
50-54	1,697	864	833	154,809	104,682	50,127
55-59	2,629	1,274	1,355	163,705	106,264	57,441
60-64	3,726	1,694	2,032	132,936	79,257	53,679
65-69	4,977	2,185	2,792	87,523	46,855	40,668
70-74	5,952	2,346	3,606	56,676	27,922	28,754
75-79	6,146	2,268	3,878	30,416	14,733	15,683
80-84	5,135	1,785	3,350	12,517	6,658	5,859
85 & over	3,881	1,239	2,642	1,327	738	589

Source: Estimated by the Statistical Bureau of the Metropolitan Life Insurance Company.
Tables 1 and 7, Appendix B

References 11 and 12.

and number of children. Once the production relationships are identified, the average wage for each productive activity in the market is applied (End note 6).

Morbidity and mortality losses among diabetic housewives are presented in Table 5. Our estimates indicate that 20,691 work-years and $64.9 million will be lost in the household for 1975. With respect to earnings lost, losses incurred by housewives are 40% of the total losses incurred by all productive diabetic females. In terms of work-years lost, housewives account for 63% of the total work-years lost by employed diabetic females and diabetic housewives. The lower earnings loss reflects the lower monetary value placed on household activities.

4) Disabled Diabetics: The remaining segment of the diabetic population for which productivity losses must be calculated is the group of totally disabled diabetics who would have been employed had diabetes not interfered. Disabled diabetics are here divided into those who are institutionalized and those who are non-institutionalized.

Work-years and earnings lost for institutionalized diabetics were estimated by taking the number of diabetics in nursing care homes and then computing the expected number who would have been employed. The estimated number of work-years lost in 1975 is 24.7 thousand, while earnings lost amount to $235.5 million (End note 7)(Table 20). According to the Diabetes Source Book (13), 5.6% of all diabetics are totally disabled (End note 8). The number of totally disabled non-institutionalized diabetics is shown in Table 21. Estimated work-year and earning losses for non-institutionalized diabetics totally disabled are 81.5 thousand and $996 million respectively.

The earning losses for totally disabled diabetics are $1.23 billion, which is·approximately 90% of the total indirect cost of diabetes excluding lifetime earning losses. This is comparable to the indirect cost estimates in the Diabetes Source Book (13) for 1967, where disabled diabetics accounted for 68% of the total indirect cost excluding lifetime earnings (End note 9).

A summary of the indirect costs estimates is provided in Tables 6 and 7. According to our estimates, 163,720 productive work-years will be lost in the United States for 1975. This translates into an earnings loss of $1,757,956,000 only when the annual mortality cost is included. As previously stated, disabled diabetics account for a significant percentage of this figure: about 70% of the earnings and 64% of the work-year losses. Employed diabetics account for 26% of the earnings and 22% of the work-year losses, with the remainder attributed to housewives.

Table 5

Work-years and earnings loss due to diabetic morbidity and annual mortality for women keeping house in the United States by age, sex and percentage distribution

(Estimated 1975)

| Age Group | Morbidity | | Annual Mortality | |
	Work-years Loss	Earnings Loss (in $1,000)	Work-years Loss	Earnings Loss (in $1,000)
16-24	338	2,284	8	54
25-44	1,047	7,578	149	1,078
45-54	1,881	11,590	273	1,682
55-64	1,724	6,983	830	3,362
65-74	3,759	8,544	2,207	5,016
Over 75	4,661	10,594	3,814	8,669
All Ages	13,410	47,573	7,281	17,338
		Percentage Distribution		
16-24	2.5	4.8	.1	.3
25-44	7.8	15.9	2.0	6.2
45-54	14.0	24.3	3.7	9.7
55-64	12.8	14.6	11.3	19.3
65-74	28.0	17.9	30.3	28.9
Over 75	34.7	22.2	52.3	50.0
All Ages	· 100.0	100.0	100.0	100.0

Note: Derived from Tables 3,4,5,6 Appendix B.

Table 6

Summary of work-years and earnings loss due to diabetic morbidity and annual mortality by type of diabetic and percentage distribution in the United States

(Estimated 1975)

	Number of Diabetics	Morbidity		Annual Mortality		Total	
		Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)	Work-year Loss	Earnings Loss (in $1,000)
Employed Male	1,606,056	21,596	$318,488	3,349	$48,493	24,945	$366,981
Employed Female	1,204,743	9,911	79,259	1,940	14,922	11,851	94,181
Women Keeping House	1,483,957	13,410	47,573	7,281	17,338	20,691	64,911
Institutionalized Diabetics	24,718	-	-	-	-	24,718	235,489
Totally Disabled Diabetics (Non-Institutionalized)	81,515	-	-	-	-	81,515	996,394
TOTAL	4,400,989	44,917	445,320	12,570	80,753	163,720	1,757,956
				Percentage Distribution			
Employed Male	36.5	48.0	71.5	26.6	60.0	15.2	20.8
Employed Female	27.3	22.0	17.7	15.4	18.4	7.2	5.3
Women Keeping House	33.7	29.8	10.6	57.9	21.4	12.6	3.6
Institutionalized Diabetics	.5	-	-	-	-	15.0	13.3
Totally Disabled Diabetics (Non-Institutionalized)	1.8	-	-	-	-	49.7	56.6
TOTAL	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Numbers are those who otherwise would be employed.
Non-applicable.

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TABLE 7

INDIRECT COSTS OF DIABETES IN THE UNITED STATES
(ESTIMATED 1975)

		AMOUNTS ($1000.)
EARNINGS LOSS FOR EMPLOYED DIABETICS		$ **461,162.0**
MORBIDITY	$397.747.0	
MORTALITY (ANNUAL)	63,415.0	
IMPUTED EARNINGS LOSS FOR HOUSEWIVES		$ **64,911.0**
MORBIDITY	$ 47,573.0	
MORTALITY (ANNUAL)	17,338.0	
IMPUTED EARNINGS LOSS FOR INSTITUTIONALIZED DIABETICS		$ **235,489.0**
IMPUTED EARNINGS LOSS FOR DISABLED (NON-INSTITUTIONAL) DIABETICS		$ **996,394.0**
LIFETIME EARNINGS LOSS FROM MORTALITY OF DIABETICS		$**1,065,573.0**
TOTAL INDIRECT COST		$**2,823,529.0**

SOURCE: ECONOMIC IMPACT WORK GROUP, 1975

When the $1,065,573,000 resulting from the discounted present value of lifetime earnings of persons who will die in 1975 is included, the total indirect cost of diabetes in 1975 will be $2,823,529,000.

b.   Direct Costs

Estimated direct costs of morbidity due to diabetes in 1975 by type expenditure are shown in Table 8. The expenditures due to diabetes for (1) hospital care, (2) physicians' services, (3) drugs, (4) nursing home care, and (5) medical professional services other than by physicians and dentists are derived from the estimated aggregate national health expenditure for each of the five categories by allocating a certain percentage of the total cost as being attributable to diabetes. The aggregate national health expenditures by type of expenditure are prepared by the Social Security Administration. However, the latest available figures are those for 1973, and it therefore was necessary to make estimates for 1975 (End note 10); they are shown in Table 22.

1)   Hospital Care: Care of diabetic patients for short-term hospitalization cost $1,050 million in 1975. This figure was based on the 1973 proportion of the total number of days of in-patient hospital care due to diabetes (2.2%) estimated from data supplied by the Hospital Discharge Survey Branch of the National Center for Health Statistics (14) and published in the Monthly Vital Statistics Reports. The Hospital Discharge Survey is a continuing probability sample of all short-term hospitals in the nation excluding military and Veterans Administration hospitals and hospital units of institutions. By definition, short-term means under 30 days' average stay per discharge. Patients were tabulated according to the diagnosis listed first on the summary sheet of the patients' records. The percentage of total days of care provided to diabetic patients in 1973 was applied to the amount of hospital care expenditures for all illnesses (Table 22) to yield the estimated amount of hospital care expenditures due to diabetes. Data from 1973 were used because they were the latest available and because this percent has remained relatively stable in recent years. This method assumes that the estimated expenditures for hospital care are distributed by diagnosis similar to the distribution of hospital days of care by first-listed diagnosis.

2)   Physicians' Services: The estimated cost of physicians' treatment of diabetic patients in 1975 was $590 million. This represents about 40 million visits to physicians. The National Disease and Therapeutic Index (15) estimated the total number of patient visits to physicians in private practice and the number due to diabetes. Its

TABLE 8

ESTIMATED DIRECT COSTS OF MORBIDITY DUE TO DIABETES BY TYPE OF EXPENDITURE, UNITED STATES, 1975*

TYPE OF EXPENDITURE	AMOUNT (IN MILLIONS)
TOTAL	2,520
HOSPITAL CARE	1,050 +
PHYSICIANS' SERVICES	590 +
DRUGS	300 **
NURSING HOME CARE	520
OTHER MEDICAL PROFESSIONAL SERVICES	60

*EXCLUDES EXPENDITURES FOR DENTISTS' SERVICES, EYEGLASSES AND APPLIANCES, PREPAYMENT AND ADMINISTRATION, GOVERNMENT AND OTHER HEALTH SERVICES, RESEARCH AND MEDICAL FACILITIES CONSTRUCTION.

+BASED ON DAYS OF CARE IN SHORT-STAY HOSPITALS

‡COST OF PATIENT VISITS TO PHYSICIANS.

**COST OF PATIENT VISITS TO PHYSICIANS FOR WHICH DRUGS WERE PRESCRIBED.

SOURCE: ESTIMATED BY THE STATISTICAL BUREAU OF THE METROPOLITAN LIFE INSURANCE COMPANY.

estimate is based on a continuing study of private medical practice in the United States in which data are obtained from a representative sample of physicians who report case history information on private patients seen over a period of time. The percentage of the estimated total patient visits of physicians due to diabetes in 1974 (2.8%) was applied to the total amount of expenditures for physicians' services (Table 22) to yield the estimated amount of expenditures due to diabetes. The assumption is that the estimated expenditures for physicians' services are distributed by diagnosis similar to the distribution of patient visits to physicians by diagnosis.

3) ·Drugs: In 1975, the expenditure for drugs by diabetic patients was $300 million. Estimates of patient visits to physicians in which medication was prescribed were reported by the National Disease and Therapeutic Index for the year 1974. The percentage of total visits in which medication was prescribed that was due to diabetes (2.8%) was then applied to the total amount of expenditures for drugs in 1975 to yield the estimated amount of expenditures due to diabetes.

4) Nursing Home Care: Nursing home expenditures in 1975 for the care of diabetic patients were $520 million. A survey by the National Center for Health Statistics in 1973-74 (16) showed the prevalence and distribution of chronic conditions among residents of nursing and personal care homes. The estimated percentage of diabetes conditions among these residents (6.0%) was applied to the total expenditures for nursing home care in 1975, and a crude total expenditure for nursing home care for diabetics was computed.

5) Other Medical Professional Services: Expenditures for other medical professional services rendered to diabetics in 1975 were $60 million. These expenses include the cost of services provided other than by physicians and dentists. The proportion of costs in this category that was due to diabetes (2.7%) in 1975) had to be estimated by applying the percentage of the combined expenditures for hospital care, physicians' services, and drugs and nursing home care to the total expenditures for other medical professional services.

The total direct costs of morbidity due to·diabetes in 1975 are estimated to be approximately $2.52 billion. Thus, the overall cost of diabetes in 1975, without attempting to measure the impact of complications of the disease, will be approximately $5.34 billion. This is the sum of the indirect cost, $2.82 billion, and the direct cost, $2.52 billion.

c. Cost of Complications

        Correlation in and of itself does not imply causation.
However, the wide prevalence of complications among diabetics does
raise certain questions about the appropriate methodology for estimat-
ing the overall cost of diabetes. A National Health Interview Survey
conducted in fiscal year 1965 found that 80% of all diabetics inter-
viewed suffered from at least one other additional chronic condition,
and 57% had three or more chronic conditions (17). Specifically, 21%
of the diabetics suffered from heart disease, 17% from high blood
pressure, and 7% were totally blind. With respect to hospital care
expenditures, diabetics with complications (all ages) stayed three
days longer per hospital visit (at an additional cost of $333) than
diabetics without complications. The average length of hospital stay
and average cost per stay for diabetics with and without complications
are shown in Table 9.

        If it is assumed that other chronic conditions present in
diabetics, such as heart disease and hypertension, are caused by dia-
betes, then the additional cost incurred from these complications
should be included in the cost of diabetes. Cost estimates based on
this assumption are provided for medical care expenditures.

        Estimation Procedures: Estimates of the cost of complica-
tions must be interpreted with some caution. First, the inclusion of
complications is predicated on the assumption that diabetes is the
direct cause of the complications and not the obverse. As pointed
out in a comprehensive report, "Diabetes is People" (18), by Dr. George
K. Tokuhata, the direction of causation between diabetes and other
chronic conditions is not always clear:

        It is common knowledge that diabetics develop a
        multitude of complications. While some of these
        complications may be considered more significant
        than others, cause-and-effect relationships are,
        in many cases, not clearly understood.

        Second, accurate and complete data on complications are
scarce. The methodology used here to compute the cost of complications
(other chronic conditions) among diabetics is based on the economic
concept of marginal cost, which is defined as the change in cost re-
sulting from the change in some other pre-defined parameter. The
estimated hospital cost component (Table 9) shows that diabetics with
complications stay an average of three hospital days longer than
diabetics without complications. The increment cost of the complica-
tions with respect to hospital care is equal to the three additional
patient days times the number of diabetics with complications who

Table 9

Average length of hospital stay: Diabetics
with and without complications

Age	Without Complications		With Complications	
	Average Stay	Average Cost Per Stay	Average Stay	Average Cost Per Stay
0-19	7.18	$ 775	8.13	$ 878
20-34	7.48	807	8.91	962
35-49	9.44	1,019	11.07	1,195
50-64	10.53	1,137	12.47	1,346
65+	12.55	1,355	14.21	1,534
All ages	9.40	$1,021	12.60	$1,354

Source: Reference 19.

received hospital care. The total number of diabetic hospital discharges is published in Monthly Vital Statistics Report. The proportion of diabetics with complications who received hospital care was determined by taking the ratio of diabetic admittants with complications to total diabetic admissions (79%) published in the Hospital Utilization Project Report (19, End note 11). The cost of complications for hospital care is equal to the number of diabetic admittants with complications times the additional length of hospital stay times the average cost per patient day.

Given adequate data, we could compute the cost of complications for the other cost components. Since these data are not available, the ratio of the hospital care cost of complications to the hospital care cost for diabetes was used to determine the cost of complications for the other types of direct medical expenditures. Because of lack of data, the indirect cost of complications could not be estimated. The cost estimates for complications are shown in Table 10.

The total direct cost is $297 million. The largest component of this is the cost of hospital care, $165 million. Physicians' services amount to $45.4 million; nursing home care, $36.1 million; drugs and sundries, $39.7 million; and other professional services, $9.9 million.

In view of the fact that estimates cannot be made for the total cost of complications, the partial cost was not included in the calculation of the overall economic impact of diabetes. Since the direct cost alone is almost $300 million, however, the total cost of diabetes including the indirect cost of complications will undoubtedly be well over $5 billion. This is especially true if one considers that the under-reporting of diabetes on the death certificate results in a significant understatement of the annual impact of mortality, as well as of the present value of future earnings.

3. SUMMARY AND CONCLUSIONS

Diabetes is an increasingly important public health problem. When the annual cost of diabetes to the United States economy was estimated in 1967, the total was approximately two billion dollars. The current estimate, excluding the impact of complications, is $5.34 billion, an increase of two and one half times in eight years. It should be emphasized again that this total must be considered minimal because of the difficulty in estimating the impact of complications of the disease. The true cost approaches $6 billion.

The economic impact represents the potential benefit to the economy if diabetes could be eliminated. It is essential that the cost of

TABLE 10

DIRECT COST OF COMPLICATIONS AMONG DIABETICS IN THE UNITED STATES
(ESTIMATED 1975)

	AMOUNT ($1,000)
TOTAL DIRECT COST OF COMPLICATIONS	$297,000
HOSPITAL CARE	$165,000
PHYSICIAN SERVICES	45,400
NURSING HOME CARE	36,100
DRUGS AND SUNDRIES	39,700
OTHER PROFESSIONAL SERVICES	9,900

SOURCE: ECONOMIC IMPACT WORK GROUP, 1975

eliminating diabetes or of taking graduated steps toward elimination
of the disease be measured so that a judgment can be made as to how
much of that expenditure should be provided by public funding.

E. END NOTES

1. The work-years and earnings lost for mortality pertain to annual
    losses in 1975. Lifetime losses are not included in these figures,
    but are considered separately.

2. The indirect cost of diabetes is relevant only to those diabetics
    who would have been engaged in productive activity had diabetes
    not interfered.

3. Because of the pressure of frictional and structural unemployment,
    a 100% rate of employment is not attainable. Therefore, 4% un-
    employment is assumed to be full employment.

4. These figures were computed by obtaining the June 1, 1975, estimate
    of the resident population of the United States from the population
    division of the Bureau of Census (20), and allowing for a monthly
    increment of 135,000 inhabitants from June 1 to July 1. This
    yielded a July 1, 1975, national estimate of the resident population
    of 213,100,000. Next, the 1974 (the latest available) provisional
    death rate from diabetes (17.4 per 100,000 population) obtained
    from the Monthly Vital Statistics (11) report was applied to the
    July 1 estimate of the resident population to yield approximately
    37,000 deaths from diabetes. The deaths were then distributed by
    age and sex as per the 1973 distribution of diabetes deaths by age
    and sex (the latest available) received from the Vital Statistics
    Division of the National Center for Health Statistics (12).

5. The other two most common methods of imputing a wage to household
    activities are: (1) applying the wages of domestic workers to
    housewives; and (2) the opportunity cost approach, which uses the
    wages for employed females in the same age categories for
    evaluating housewives' services.

6. The average economic value of women keeping house for 1972 by age,
    adjusted for number of children, was supplied by W.S. Brody, SSA.
    These figures are shown in Table 15.

7. The nursing home figures for diabetics are for 1969. These were
    adjusted upward on the basis of the average annual increases in
    nursing home residents from 1963 to 1970 -- 11.8%.

8. The 5.6% rate applies only to non-institutionalized diabetics.
    This rate was applied to our diagnosed diabetic population over
    age 45.

9. From the Diabetes Source Book: indirect cost excluding lifetime
    earnings was $644 million. Cost for those unable to work was
    $442 million.

10. These figures were derived by adding to the 1973 annual estimates
    from the Social Security Administration (21) the increments
    between fiscal year 1973 and 1974 (22) from the same office, to
    yield a provisional estimate for calendar 1974. The annual esti-
    mates for 1973 and the provisional annual figures for 1974 were
    linear-extrapolated to 1975 and rounded.

11. Hospital Utilization Project of Pittsburgh, Pennsylvania, collects
    data from 169 member hospitals in Pennsylvania and surrounding
    states. For 1973, the number of diabetic persons was 16,900,
    of whom 13,300 (about 79%) were listed with multiple diagnoses.

F. APPENDIX A
ESTIMATION PROCEDURES

1. INDIRECT COSTS

   a. Earnings -- calculations for earning losses for employed dia-
betics due to morbidity and annual mortality wages by age and sex for
March of 1973 were taken from the Current Population Report "Money
Income in 1973 of Families and Persons in the United States." The
mean income figures were used because these figures correspond to the
expected value of earnings. The earnings figures were adjusted to
1975 by using a 6% rate per annum obtained from regression analysis
for the period 1950-1972.

   b. Population -- the diabetic population was determined by apply-
ing prevalence rates obtained from National Center for Health Statistics
and the Diabetes Source Book. For undiagnosed diabetics, prevalence
rates were not provided for males and females. After determining the
total number of undiagnosed diabetics, the number of male and female
undiagnosed diabetics was determined by assuming that diagnosed and un-
diagnosed diabetics had similar distribution with respect to male-
female breakdown.

   c. Disabled Diabetics Non-institutionalized -- in the report
published by HEW, "Diabetes Source Book," 5.6% of the diabetics in-
cluded in that study were totally disabled. An examination of restricted
activity days among diabetics revealed that 92% of all restricted
activity days were accounted for by diabetics over age 45. Based on

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this information, it seemed probable that most of the disabled diabetics would be over 45. The non-institutionalized totally disabled diabetic population was obtained by applying the 5.6% rate to the diabetic population over 45. The expected number of employed diabetics was then obtained by multiplying this population by labor force participation rates and 4% unemployment rate.

d. <u>Institutionalized Diabetics</u> -- this group was obtained by taking the number of diabetics in nursing homes in 1969, as published by NCHS in "Chronic Conditions and Impairments of Nursing Home Residents," and adjusting the figures to 1975 on the basis of the average percentage increase in nursing home residents between 1963-1975 (11.85%).

e. <u>Housewives</u> -- the number of diabetic housewives in 1975 was estimated by taking the percentage of women keeping house to total families in 1973, as published in the "Handbook for Labor Statistics," and applying these figures to our population estimates for 1975 to give the number of housewives in 1975. Applying the diabetic prevalence rates for females to this total provided an estimate for the diabetic housewives in 1975.

f. <u>Morbidity Losses</u> -- with the exception of housewives, the procedure for estimating morbidity losses was to multiply the average earnings figure by age and sex times the number of work-years lost in each age-sex diabetic cohort. The number of work-years lost by cohort was derived by multiplying the work-loss days per diabetic per annum times the number of diabetics in each cohort and assuming a 250 day work-year. For housewives, the earnings figures used were those provided by Wendyce Brody in the Social Security Administration (see 2, Table 1). These figures are based on the market value of household services.

g. <u>Mortality Losses</u> -- annual mortality losses were computed by taking one-half the number of deaths times the appropriate income figure for each group.

2. <u>COST OF COMPLICATIONS</u>

The cost of complications was computed for only medical care expenditures. The procedure consisted of:

a. Computing the difference in average length of stay for diabetics with and without complications (three days per stay).

b. Next, we took the total number of diabetics in short-stay hospitals from the Hospital Discharge Survey (discharges = 526,728).

c. To estimate percent of diabetics in short-stay hospitals, we used figures from HUP report, which had 78.9% of diabetics in hospitals listed with multiple diagnoses.

d. Multiplying the average cost per patient day adjusted ($124) (23) times number of diabetics times three patient days gave us the complication cost for hospital care.

e. For the other medical care component, we used the ratio of hospital care cost for complications to total hospital care cost for all diabetics (15.2%).

G. APPENDIX B
BACKGROUND TABLES

Table 21. Number of Totally Disabled Noninstitutionalized Diabetics in the United States (Estimated 1975)

Table 22. Aggregate National Health Expenditure by Type of Expenditure, United States, 1973 and Estimated 1975

H. FUTURE DIRECTIONS

1. GOAL

The broad goal should be to determine the full economic impact of diabetes including the complications of the disease.

2. SPECIFIC OBJECTIVES

Specific objectives should be to develop the data base necessary to estimate costs more accurately.

3. APPROACHES

Projects for the future should include the following:

a. The development of a profile of diabetics with and without complications. This profile should contain information on:

   1) Socioeconomic characteristics

      a) Age
      b) Sex
      c) Income
      d) Education
      e) Occupational status

   2) Morbidity and mortality rates

      a) Work-loss days
      b) Disability days
      c) Deaths

   3) Medical care utilization

      a) Days of hospital care
      b) Number of physician visits
      c) Use of drugs

4) Status of diabetics

    a) Disabled in institutions
    b) Disabled at home
    c) Employed
    d) Housewives

b. A cost-benefit analysis of current programs that have as their objective the modification or elimination of diabetes. Determine from an economic viewpoint whether some programs should be expanded and some contracted or eliminated.

c. A cost-benefit analysis of future programs designed to reduce diabetes prevalence by some percentage, e.g., 50%.

4. PROJECT SUMMARIES (See project summary sheets attached.)

a. Economic impact of diabetes including complications of the disease.

b. Cost-benefit analysis of current and future diabetes programs.

PROJECT SUMMARY SHEET

PROJECT TITLE: ECONOMIC IMPACT OF DIABETES INCLUDING COMPLICATIONS
                 OF THE DISEASE

OBJECTIVE: Determine the full economic impact of diabetes,
                 including the complications of the disease.

APPROACH TITLE:

     A workgroup should be designated to set the guidelines for
     appropriate data to be collected.

DESCRIPTION OF PROJECT:

     The workgroup should determine what associated conditions are
     considered complications of the disease and collect data for
     these conditions when they are associated with diabetes. Data
     to be collected should include: (a) socioeconomic character-
     istics; (b) morbidity and mortality rates; (d) medical care
     utilization; (d) work status.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

     1. Constitution of workgroup.
     2. Provision of funds and personnel to support workgroup
         activities.
     3. Development of standards to define complications of
         diabetes.
     4. Determination of types of data to be collected.

PRESENT STATUS:

     A great deal of data is being collected relating to diabetes as
     a primary cause of morbidity and mortality, but there are de-
     ficiencies in multiple cause analysis. Separate statistics are
     collected for conditions that may be considered complications of
     diabetes, but their impact as part of the total diabetes picture
     has not been adequately established.

The workgroup must determine the conditions that are complications of diabetes. This is especially difficult with regard to macro-angiopathy. For example, if all cases of coronary artery disease are not to be considered as complications of diabetes, what would a valid percentage be when those conditions occur concurrently?

FORM OF RESULTS:

Tabulation of economic impact of diabetes including complications should be included in the proposed quinquennial "Diabetes Source Book."

PROJECT SUMMARY SHEET

PROJECT TITLE: COST BENEFIT ANALYSIS OF CURRENT AND FUTURE DIABETES
                 PROGRAMS

OBJECTIVE: A cost benefit analysis of current and future programs
                 that have as their objective the modification or
                 elimination of diabetes.

APPROACH TITLE:

   A workgroup should be designated consisting of diabetologists and
   economists.

DESCRIPTION OF PROJECT:

   Diabetes programs that are aimed at elimination or modification
   of diabetes should be defined. These programs should then be
   subjected to cost analysis. The size of the investment needed
   to eliminate or partially eliminate diabetes will be measured
   against the potential cost benefit to determine the expected
   net benefits that can be achieved.

KEY EVENTS CRITICAL TO THE
   SUCCESS OF PROJECT:

   1. Constitution of workgroup.
   2. Provision of funds and personnel to support workgroup
       activities.
   3. Definition of programs aimed at eliminating or modifying
       of diabetes.
   4. Determination of criteria to measure cost of these programs.

PRESENT STATUS:

   The economic impact of diabetes which has been measured is the
   benefit portion of a cost benefit analysis in that it defines the
   potential benefit that can be achieved if diabetes is eliminated.
   The cost of programs to eliminate or modify the disease has not
   been adequately measured.

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The workgroup must determine the programs that have as their objective the elimination or modification of diabetes. Techniques must be developed that will measure the cost of programs and perform a cost benefit analysis.

FORM OF RESULTS:

A periodic report of the workgroup.

TABLE 11

ESTIMATES OF UNITED STATES POPULATION
BY AGE AND SEX - 1975

	UNITED STATES		
Age Group	TOTAL (in 1,000)	MALES (in 1,000)	FEMALES (in 1,000)
Under 16	58,046	29,612	28,434
16 - 24	35,715	17,891	17,824
25 - 44	53,495	26,267	27,228
45 - 54	23,747	11,472	12,275
55 - 64	19,770	9,336	10,434
65 - 74	13,879	6,027	7,852
Over 75	8,448	3,119	5,329
TOTAL	213,100	103,724	109,376

Source of basic data: References 24, 25, 20

Table 12

Prevalence rates for diagnosed and undiagnosed diabetics by age and
sex in the United States*

Age Group	Diagnosed Diabetics			Undiagnosed Diabetics**
	Both Sexes	Male	Female	
Under 17	1.3	1.1	1.6	.7
17–44	8.9	6.9	10.8	5.2
45–64	42.6	40.6	44.4	20.6
Over 65	78.5	60.3	91.3	26.2
All Ages	20.4	16.3	24.1	8.2

* (1) Prevalence rates are % figure per 1,000 population.
 (2) For the purpose of this study, the same prevalence rates are applied
     to the sub-age groups: for instance, 40.6% prevalence rate is applied
     to both sub-age groups 45-54 and 55-64 for diagnosed male diabetics.

**Prevalence rates for undiagnosed diabetics are rates for both sexes.
 In this study, the % is divided by sexes using the weight of populations in
 in each sex to the total population.

Source: References (26) and (13).

Table 13

Labor force participation rates and diabetic work-loss days per
annum by age and sex

Age Group	Labor Force Participation Rates		Diabetic Work-Loss Days per Annum	
	Male	Female	Male	Female
16-24	69.8	52.3	2.3	0.0
25-44	95.8	51.6	2.3	2.1
45-54	93.3	53.1	3.4	2.1
55-64	79.2	41.9	3.4	1.9
65-69	36.8	15.5	5.0	1.9
Over 70	14.8	5.3	5.0	3.1
All Ages	78.4	44.1	3.2	3.1

Source: References (13) and (27).

TABLE 14

NUMBER AND PERCENTAGE OF FEMALES KEEPING HOUSE
IN THE UNITED STATES BY AGE (ESTIMATED 1975)

Age Group	Percentage of Females in Housekeeping Relative to Total Female Population. (%)	Percentage of Females in Housekeeping relative to Non-Participants in Labor Force. (%)	Number of Females in Housekeeping. (in Thousands)
16 – 24	19.4	40.6	3,457
25 – 44	42.4	87.6	11,544
45 – 54	41.1	87.6	5,045
55 – 64	49.0	84.2	5,112
65 – 69	69.0	81.6	5,417
70 and Over	77.3	81.6	4,119
All Ages	42.9	76.8	34,694

Source: References 27 and 28

Table 15

Money income of employed and market value of females keeping
house in the United States

(Estimated 1975)*

| Age Group | Money Income | | Market Value of a Housewife |
	Male	Female	
16-19	$ 5,544	$4,448	$6,359
20-24	8,490	6,218	7,159
25-34	13,093	8,161	7,572
35-44	15,880	8,168	6,905
45-54	16,145	8,071	6,162
55-64	14,882	8,117	4,051
Over 65	13,461	7,079	2,273

*Figures for 1975 estimated by applying the average rate of change of money
income from 1950-1972 (6% per annum).

Source: References (10) and (28).

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TABLE 16

DIABETIC MORTALITY: NUMBER OF DEATHS BY AGE AND SEX
IN THE UNITED STATES (ESTIMATED 1975)

| Age Group | Number of Deaths Due to Diabetes | | |
	Both Sexes	Male	Female
Under 16	114	53	61
16 – 24	174	88	86
25 – 44	1,556	863	693
45 – 54	2,710	1,380	1,330
55 – 64	6,355	2,968	3,387
65 – 74	10,929	4,531	6,398
Over 75	15,162	5,292	9,870
All Ages	37,000	15,175	21,825

Source: See Table 4

Table 17

Estimated present value of lifetime earnings by age and sex
United States, 1975

Age	Men	Women
Under 1	106,623	65,210
1-4	117,284	71,227
5-9	143,145	86,854
10-14	174,432	105,817
15-19	208,106	124,532
20-24	236,043	133,609
25-29	246,474	129,045
30-34	238,530	118,256
35-39	218,866	106,172
40-44	190,977	92,624
45-49	157,421	77,345
50-54	121,160	60,176
55-59	83,410	42,392
60-64	46,787	26,417
65-69	21,444	14,566
70-74	11,902	7,974
75-79	6,496	4,044
80-84	3,730	1,749
85 & over	596	233

Source: Computed by the Metropolitan Life Insurance Company based
on 1972 data, which reflect a 4% net discount rate and adjustments for
variations in labor force participation rates, supplied by Barbara Cooper,
Division of Health Insurance Studies, Office of Research and Statistics,
Social Security Administration.

References: 8, 29, 30.

Table 18

Estimated present value of lifetime earnings and indirect costs due to diabetes by age and sex, United States, 1975

| Age | Lifetime Earnings | | Indirect Costs (in thousands) | | |
	Men	Women	Total	Men	Women
Total			928,115	595,145	332,970
Under 1	54,364	34,564	771	598	173
1–4	61,854	39,236	753	557	196
5–9	83,039	52,602	1,348	664	684
10–14	111,297	70,491	4,371	2,115	2,256
15–19	154,059	89,918	7,807	4,930	2,877
20–24	174,786	101,669	16,937	10,837	6,100
25–29	190,797	100,917	36,119	26,330	9,789
30–34	190,574	94,303	45,215	31,635	13,580
35–39	179,732	86,492	58,092	42,956	15,136
40–44	160,916	77,233	72,887	51,493	21,394
45–49	135,974	66,044	102,987	70,163	32,824
50–54	107,298	52,573	136,498	92,705	43,793
55–59	75,613	37,744	147,474	96,331	51,143
60–64	43,059	23,885	121,476	72,942	48,534
65–69	20,205	13,268	81,192	44,148	37,044
70–74	11,032	7,363	52,432	25,881	26,551
75–79	6,063	3,789	28,445	13,751	14,694
80–84	3,581	1,681	12,023	6,392	5,631
85 & over	579	216	1,288	717	571

Source: Same as Tables 4 and Table 7, Appendix B.

Table 19

Present value of lifetime earnings by age and sex (1972)

Age	Males		Females	
	4%	6%	4%	6%
< 1	95,553	48,720	58,439	30,976
1 - 4	105,107	55,433	63,832	35,163
5 - 9	128,283	74,418	77,836	47,141
10-14	156,322	99,742	94,830	63,172
15-19	186,500	129,394	111,603	80,583
20-24	211,537	156,640	119,737	91,114
25-29	220,884	170,988	115,647	90,439
30-34	213,765	170-788	105,979	84,513
35-39	196,143	161-072	95,149	77,513
40-44	171,149	144,209	83,008	69,215
45-49	141,077	121,856	69,315	59,187
50-54	108,581	96,158	53,929	47,115
55-59	74,750	67,763	37,990	33,826
60-64	41,930	38,589	23,674	21,406
65-69	19,218	18,107	13,054	11,890
70-74	10,667	9,886	7,146	6,598
75-79	5,822	5,434	3,624	3,396
80-84	3,343	3,209	1,567	1,507
85 >	534	519	199	194

Source: Preliminary data from the Division of Health Insurance Studies,
         Office of Research and Statistics, Social Security Administration.

From: Barbara Cooper

Reference 8.

Table 20

Number of institutionalized diabetics in the United States

(Estimated 1975)

Age Group	Number of Diabetics*		
	Both Sexes	Male	Female
Under 65	8,537	5,156	3,381
65-74	7,765	3,977	3,788
Over 75	8,416	4,116	4,300
All ages	24,718	13,249	11,469

*Figures are the diabetics who, otherwise, would be employed. These figures are calculated by applying the labor force participation rates and full-employment rates to the total number of institutionalized diabetics.

Source: Reference 31.

Table 21

Number of totally disabled noninstitutionalized diabetics
in the United States (Estimated 1975)

Age Group	Both Sexes	Male	Female
45 – 54	56,598	26,078	30,520
55 – 64	47,151	21,213	25,938
65 – 74	60,491	20,350	40,141
Over 75	37,757	10,520	27,237
Total	201,997	78,161	123,836

* Number of totally disabled diabetics is obtained by applying 5.6% to the number of diagnosed diabetic population over 45.

Source: Reference 13.

Table 22

Aggregate national health expenditure by type of expenditure, United
States, 1973, and estimated 1975

Type of Expenditure	Amount in millions	
	1973	1975
Total	$99,069	$115,000
Health Services and Supplies	92,327	
Hospital care	38,270	47,700
Physicians' services	18,200	21,200
Drugs and drug sundries	9,300	10,800
Nursing home care	7,050	8,600
Other professional services	1,900	2,300
Dentists' services	5,970	
Eyeglasses and appliances	2,091	
Prepayment and administration	3,998	
Government public health	1,905	
Other health services	3,643	
Research and Medical Facilities Construction	6,742	
Research	2,484	
Construction	4,258	

Source: 1973: Social Security Administration: Research and Statistics.
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   1929-73, February 19, 1975.
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X. HEW ORGANIZATIONAL CHART
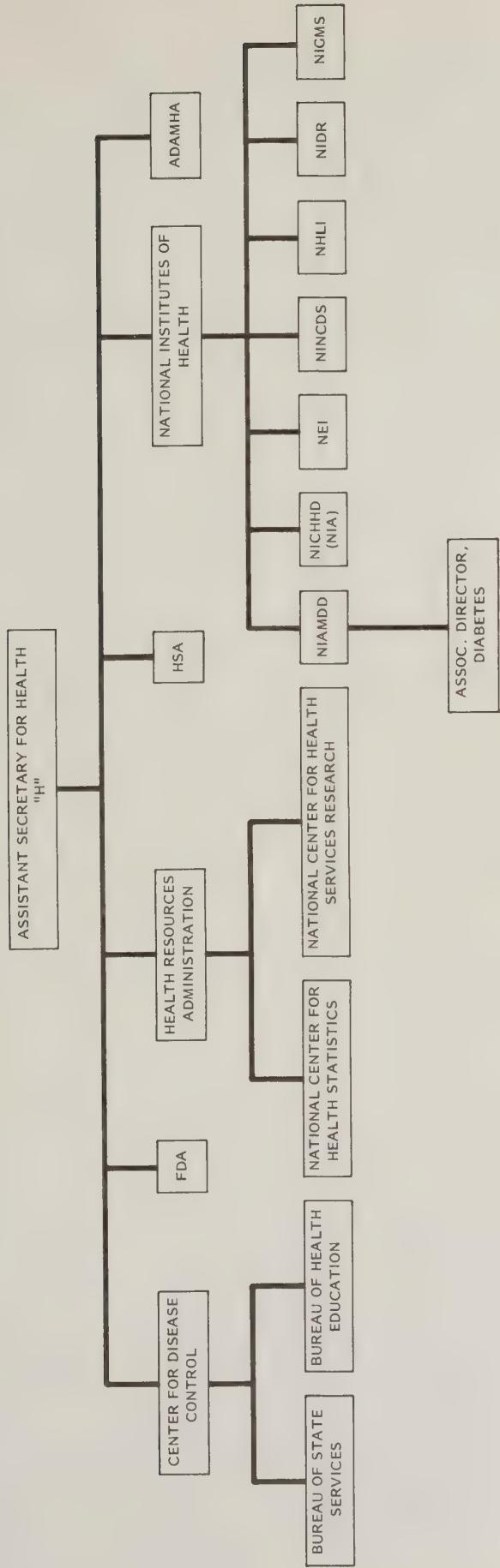
ORGANIZATION CHART - "H"
COMPONENTS OF SPECIAL INTEREST TO
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Report of the

National Commission on Diabetes

to the Congress of the United States

Volume III

REPORTS OF COMMITTEES, SUBCOMMITTEES,

AND WORKGROUPS

Part 3

ETIOLOGY AND PATHOLOGY OF DIABETES

"The National Diabetes Mellitus Research and Education Act" (Public Law 93-354), signed by the President on July 23, 1974, directed the appointment of a National Commission on Diabetes whose charge was to formulate a long-range plan of research and education to combat diabetes mellitus. The Commission submitted its report to Congress on December 10, 1975.

REPORT OF THE NATIONAL COMMISSION ON DIABETES

Report of the

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to the Congress of the United States

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Volume III

REPORTS OF COMMITTEES, SUBCOMMITTEES, AND WORKGROUPS

Part 3

ETIOLOGY AND PATHOLOGY OF DIABETES

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VOLUME III

REPORTS OF THE COMMITTEES,
SUBCOMMITTEES, AND WORKGROUPS

PART 3

Report of the Committee on
Etiology and Pathology of Diabetes

Report of the

COMMITTEE ON THE ETIOLOGY AND PATHOLOGY

OF DIABETES

to the

National Commission on Diabetes

Co-Chairmen:

George F. Cahill, M.D.

Paul E. Lacy, M.D., Ph.D.

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I. INTRODUCTION

Nine workshops were held under the auspices of the Committee on the Etiology and Pathology of Diabetes utilizing members of the Commission as well as over 100 consultants from the United States and abroad. These workshops were as follows:

Diabetic Neuropathy	New York, Jan. 4-5
Obesity and obesity centers	New York, Jan. 18
Diabetic Retinopathy	Bethesda, June 23-24
Genetics, viruses, and animal models	Atlanta, July 8-9
Islet transplantation and mechanical devices	Atlanta, July 9-10
Insulin production and metabolic effects	Bethesda, July 28-30
Microangiopathy and macroangiopathy	Bethesda, August 11 -13
Dental problems of diabetes	Bethesda, September 9
Perinatal problems of diabetes	Bethesda, September 10

The recommendations of this Committee are included among those appearing in Volume One of the Commission's Report, and they, therefore, are not reproduced here. The basis of these recommendations, however, was the extensive work done by the consultants in the various workgroups, and the Committee takes sincere pleasure in presenting the following summaries of their findings to the Commission.

II. SUMMARY OF WORKSHOP ON
DIABETIC NEUROPATHY

A. DIABETIC NEUROPATHY

When one speaks of the "specific" complications of diabetes in
man, the term "triopathy" is applied to the pathological involvements
of the eye (the "retinopathy"); of the kidney (the "nephropathy");
and of the nervous system (the "neuropathy"). The nervous system in
the diabetic patient is affected in a number of different ways.
Firstly, the increased or accelerated atherosclerosis of the diabetic
patient augments the risk of developing stroke at approximately twice
that of the nondiabetic population. Abnormal vessel closure may also
occur elsewhere, such as in the spinal cord or the nerve roots, how-
ever these are rare but tragic events. The term "neuropathy" is
usually applied to a diverse number of problems which are almost
unique to the diabetic patient, but which occur in 100% of all of
these patients and it describes abnormalities occurring in nerves
outside of the brain and spinal cord.

B. NERVE STRUCTURE

Peripheral nerves are unique compared to other tissues in that
the body of the cell, where many of the important reactions such as
synthesis of new proteins occur, may be literally several feet from
the end of the cell. These synthesized materials must be transported
along and through the body of the cell - the axon. Thus a single nerve
axon connecting the spinal cord to the feet transverses the entire leg,
exposing its membrane to toxic influences and metabolic alterations.
It is no surprise that these long thin filaments are exquisitely
affected by vitamin deficiences, poisons such as lead and alcohol, or
diseases such as diabetes or uremia (renal failure), and particularly
by simple aging. Along the course of the axons are supplementary
cells, the Schwann cells, which in certain large axons literally wrap
the nerve in an insulating membrane of a fatty protein, myelin. Each
single Schwann cell about these axons wraps the nerve for about 1/20th

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of an inch and interpersed between each "sausage link" between the Schwann cell and its myelin is a junction, or "node of Ranvier." In smaller axons, the myelin is not apparent, but the ever present Schwann cells may still be playing an important, but as yet poorly defined, role in the maintenance of the nerve cell itself, perhaps by helping nutritionally.

C. CLINICAL PROBLEM

Literally 100% of diabetic patients have one or more demonstrable alteration in their peripheral nerves. About 1/4 will have symptoms and in about 1/2 of these the symptoms are of sufficient consequence to cause various degrees of partial to total disability. The most common pattern is the "Mixed distal polyneuropathy." This involves a number of different nerves supplying the peripheral tissues, mainly to the lower limbs, and effects mainly sensation leading, as the lesion progresses, to total anesthesia. However, in many patients, and these are usually those in their middle age and older, there may be excruciating and totally disabling pain for from months to a year or two, occasionally requiring opiates for relief. As sensation decreases, the pain and sensation dissapear leaving an anesthetized extremity which tragically is prone to all varieties of injury such as ulceration and eventual loss, particularly if the limb is also affected by accelerated atherosclerosis which it usually is.

The autonomic nervous system is also involved in literally all diabetic patients but significant symptoms are caused in about 1/10th of the subjects, and again, these are more frequent in the middle-aged diabetic patient. Since this "vegetative" nervous system involves many basic functions, such as movement of food through the gastrointestinal tract, contraction of the urinary bladder, opening of the urethral valves responsible for initiation and termination of urination, and, in the male, erection and ejaculation, the sequelae of autonomic neuropathy are manifold. Approximately 1% of diabetic patients may have episodes of nocturnal diarrhea and an equivalent number may be unable to urinate, necessitating either surgery or intermittent catheterization.

D. PATHOLOGY

Because of the non-fatal nature of this group of complications and the extreme difficulty in tracing peripheral nerves through tissues -- a "needle-in-the-haystack" problem -- there are only two or three studies, mainly by Thomas in England and Asbury in this country, which show in diabetic patients a scattered loss of Schwann cells and

their myelin about myelinated axons, termed "segmental demyelinization." Since the smaller axons, those involved in sensations, or the autonomic nerves, may lack the myelin, they usually cannot even be found in either the diabetic or non-diabetic; therefore our knowledge of the pathology of these cells in the diabetic patient is essentially zero. The basic physiologic interrelationships between the Schwann cells, the axons of the nerve cells, and the nerve cell viability and function is not known, nor is it known whether the primary lesion in the diabetic patient is in the axon, or in the Schwann cell, or possibly in the myelin, which is supposedly produced by the Schwann cell, Thus, knowledge of the fundamental physiology, not to mention the pathology, is at a very primitive state. It is known that the rate at which the larger myelinated fibers conduct electrical impulses becomes delayed literally within weeks to months after the development of diabetes in man and experimental animals, and in man (and animals) this can now be partially corrected or prevented by insulin or other metabolic manipulations (vide infra).

E. NEW DEVELOPMENTS

At least three routes of investigation are currently in progress by an almost infinitesimally small number of investigators, numbering at most but a half dozen in the entire world, who are directing their research toward diabetic neuropathy. Spritz, in New York, has focused on the levels of myelin in diabetic nerve and found it decreased in man and experimental animals as it also does in aged man; and more recent studies in experimental diabetic animals have shown a number of metabolic deficiences, such as the rate of protein synthesis. This parallel nature between age and diabetes may explain the synergy between these two events and why the middle-aged and older diabetic patient is more susceptible to the distal polyneuropathy than the child with a more severe degree of insulin deficiency. Gabbay, in Boston, has studied the accumulation of sorbitol, an abnormal byproduct of glucose metabolism, and has correlated its accumulation with delayed nerve conduction velocity in experimentally diabetic animals, and he has been successful in using chemical agents to block the enzyme system responsible for sorbitol synthesis. Winegrad, in Philadelphia, has studied another material, myoinositol, which is similar to sorbitol but, in contrast, is deficient in diabetic nerve. When the animal is supplemented with myoinositol, the delayed nerve conduction velocity is corrected. Matschinsky, in St. Louis, has demonstrated that the rate of flow of nutrients and other materials from the cell body in the spinal cord along the axon is delayed in diabetic nerve and has suggested the "delayed axonal flow" may play a role in the etiology of diabetic neuropathy.

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Currently, workers at the NINDS and other laboratories are developing methods for culturing nerve cells and Schwann cells so that their specific metabolism, such as the formation of myelin and the overall control of this process, can be studied. The question is simply, can growing Schwann cells in the presence of a high glucose concentration alter their function or viability? Or is insulin essential for Schwann cell viability and function?

F. NEEDS

The needs are manifold. First, knowledge of the diabetic neuropathic lesion in man will require a much larger input by the morphologists, meaning more aggressive obtaining of tissues by biopsy and analysis at autopsy. In official language, morphometric studies are in great need by those few individuals capable of so doing. At present there are essentially no studies of diabetic peripheral nerves using the electron microscope, not to mention any of the recently developed more elegant techniques of scanning or freeze-etching ultra microscopy. Likewise, appropriate clinical testing by competent individuals, like Dyck at the Mayo Clinic, must be vastly expanded to study the natural history of diabetic neuropathy. We are even lacking in adequate data concerning incidence, prevalence, morbidity, and natural history of the neuropathies to use as baselines should therapeutic approaches be developed, as now seems to be the case in experimental animals. The effects of diabetes on the basic biochemical processes of the nerve cell and the Schwann cell, and the interrelations between the two cells, need be studied in far greater depth and by more than the handful of scientists currently engaged in the problem. Thus basic research in nerve tissue needs to be vastly expanded.

III. SUMMARY OF WORKSHOP ON
OBESITY

Obesity and diabetes mellitus are so intertwined socially, physiologically, and economically that to deal with one without the other is impossible. Statistics, as summarized in the reports from the Workgroup on Epidemiology of the Committee on Scope and Impact, show that over 70% of adult maturity-onset diabetic patients are overweight. It is more significant, however, that the accumulation of excess weight between the ages of 25 and 44 increases the incidence of diabetes several fold, as well as increasing mortality from diabetes.

Obesity itself is a national health problem. It is estimated that at least 20 million Americans each year are actively pursuing some course of weight reduction through diets or medications. Likewise, it is also estimated that an equivalent number consult physicians for their weight problems, and the food industry sells several billion dollars each year of putatively low calorie products to individuals concerned with calorie intake. Fat people undergo prejudice in employment, as well as being socially distinguished. The enormity of the problem prompted the Fogarty International Center of the National Institutes of Health to hold a series of meetings and to prepare an exhaustive document on the state of obesity in the United States.

At this moment, this document (Obesity in Perspective. Fogarty International Center Series on Preventive Medicine, Vol. 2, Parts 1 and 2, Bray, G.A. Editor, U.S. Government Printing Office, Washington, D.C.) is in press and will be available for mass distribution. Part 1 contains summary statements and recommendations, and Part 2 contains a series of papers detailing the present state of our knowledge in appetite physiology, energy balance, adipose tissue physiology, the psychodynamics of caloric control, and other aspects of the diagnosis, characterization, and treatment of obesity in man and experimental animals. Publication of a third and companion volume, a well-illustrated brief paper-back, is being planned which could be distributed free to schools and other institutions, such as state and county health departments, and would serve as a simple dietary guide placing the facts and therapeutic guidelines in clear perspective. In the definitive publication now in press, Section V, Chap. 36-43 deals with the interrelationships of diabetes and obesity. Consequently the Workshop on Obesity met briefly June 18 not to delve

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deeper into the pathophysiology of obesity and diabetes, but to update knowledge and to make recommendations relevant specifically to the function of the Commission. Nevertheless some summary statements are in order.

Maturity-onset type of diabetes rises and falls with the nutrition of a society. In starving populations, the disease is infrequent; in overfed populations it is endemic. Its incidence fell dramatically in Europe during World War II and subsequently returned as food again became available. Certain populations, such as those Indians in South Africa who are middle-aged, overweight, sedentary merchants, have rates as high as 30 to 40%; whereas in a similar population in India the disease is most infrequent except in the more affluent. On the other hand, the treatment of maturity-onset diabetes is primarily nutritional, and, if the subject is overweight, caloric reduction and weight loss form the basis of therapy.

Forty years ago, Ogilvie, a pathologist in Edinburgh, Scotland, noted hyperplasia of the islets of Langerhans, the insulin producing clusters of cells in the pancreas, in obese humans at autopsy. In diabetes, a reduction was noted, and, in obese diabetic patients although there might be an adequately appearing number of cells, there were still less than in obese non-diabetic persons. When the immunoassay for insulin in blood was developed by Yalow and Berson, it soon became apparent that obese individuals had higher insulin levels than the non-obese. Obese diabetic patients might even have more insulin than non-obese normals, but there still appeared to be a "relative" insulin deficiency as compared to the non-diabetic obese person. Thus, obesity appears to necessitate higher insulin levels. Many investigators, particularly Rabinowitz and Zierler, demonstrated that a given amount of insulin is less effective in an obese individual, and this is true whether the effect is measured in muscle, adipose tissue, or, as shown by Felig and colleagues, in liver. There are two hypotheses explaining the inability of insulin to work. Roth and colleagues, at the National Institutes of Health, have shown that the cell membrane, even of cells such as the circulating white blood cells, have less sites for insulin to react with on the cell membrane in those cells from obese humans or from animals experimentally rendered obese. A second hypothesis, that of Cuatrecasas, Lockwood, and colleagues at Johns Hopkins, is that the secondary processes within the cells, which are initiated by insulin reacting with the cell membrane, are defective in cells from obese animals or man. Whichever mechanism is defective, the result is that fat people need more insulin Genuth has calculated that a normal person uses 30-40 units of insulin daily and a non-diabetic fat person uses over 100 units. Thus it is logical that in an individual with a compromised insulin reserve, obesity can be very detrimental.

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Why the obesity? The recent, but now "classical," studies of Hirsch and colleagues of the Rockefeller Institute have distinguished two varieties of obesity. Simply, is obesity too many fat cells or too much fat per cell? Hirsch's studies, now corroborated by most (but not all) other investigators, have shown the number of fat cells to increase up to adolescence and that the greater the degree of nutrition is during this phase, the more fat cells are formed. The critical timing has been pushed earlier and earlier and there is now some evidence that later obesity is more prevalent in bottle-fed than breast-fed infants, the bottle-fed being forcibly overfed whereas the breast-fed relies more on physiological need. These observations also explain why the 200-300 lb. teen-ager is almost impossible to reduce in later life, since he or she has to combat continuous physiologic starvation. The type of obesity most frequently associated with diabetes appears more confined to the much more common "middle-aged" spread, an hypertrophic, not hyperplastic, obesity.

This leads to the physiology of fuel intake and storage, and the Fogarty report deals with our present knowledge in extenso. In summary, there is still much ignorance in the area. Many experimental animal data, and also data in normal man, suggest that there is some sort of overall calorostat relating food intake with caloric stores. Sim's studies on normal men force-fed to gain weight show a rapid spontaneous return to prior normal weight after the force-feeding had been terminated. Is the lesion in obese man a defective assessment of caloric stores, in other words, a lesion in the float in the gas tank? Or, is it a lesion in the gas gauge, probably located in the hypothalamus in the base of the brain? Or, is it that the driver has the appropriate signal but pays no attention to it and eats for emotional and not physiological reasons? The studies of Schachter at Columbia suggest the last-mentioned to be the principle problem. However, concordance for obesity in identical twins is high, suggesting a strong genetic input, but because few identical twins are reared apart from birth or soon thereafter, environmental vs. hereditary inputs are difficult to separate.

The studies of Coleman and colleagues in various mouse mutants have shown that one mutant animal is lacking a signal released from the peripherally stored fuel and another obese mutant possesses the signal but is unable to detect it in its appetite and satiety centers in the brain. Do these models also exist in man?

In experimental animals two areas in the hypothalamus are related to hunger and satiety, and neurophysiologists and neuroendocrinologists are actively studying their interrelationships. It is interesting that this is the only location of the brain where insulin appears to have the acute effects on glucose metabolism and

other fuels, such as fats, which can gain access here, whereas in the remainder of the central nervous system they are excluded from access by a blood-brain barrier.

The hypothalamus is the cross-road of a number of vegetative and cognitive functions, and thus it is common ground to the pure physiologists as well as those interested in behavior and the effects of emotions and other aspects of the external world upon it. The multitude of inputs, therefore, makes hard, quantitative science difficult. Also, the effects of fetal, neonatal, infantile, and childhood nutrition and the relationships of this nutrition to emotional inputs makes this fertile ground for study by the behavioral scientists in collaboration with the physiologists.

Returning to diabetes and obesity, if overweight maturity-onset type diabetic patients do have a relative insulin deficiency, therapy is simply weight reduction. But in the real world, significant decreases are achieved in only 5-10% of individuals, statistics reminiscent of cure for hard drug addiction. This failure rate necessitates a combined multidisciplinary approach to the problem. Another possibility is to clarify biochemically why there is insulin-resistance in the obese person. If the insulin affect on cells could be amplified by pharmacologic agents, the diabetes might be modified without weight loss. Thus, much basic information needs to be collected on insulin receptors, second messengers, and how obesity alters these. Again, 90% of all diabetic patients, those with the maturity-onset type of the disease, are in this category and are potentially curable by further knowledge and its application.

Present support: Currently (FY 1975) there is one Center for the study of obesity and 26 research grants dealing with the topic, totalling approximately $500,000/annum in direct support. There are fellowships available in the area of nutrition at the M.D.-Ph.D levels; however, none are directed to other health personnel such as dietitians or psychologists interested in behavior related to calorie balance. Approximately $1 million of annual support is indirectly related via studies on insulin's metabolic and biochemical effects.

NEEDS

A. BASIC

      1.   Knowledge of adipose cell kinetics and the importance of heredity and the nutritional state thereon

      2.   Knowledge of the relationship between adipose mass and caloric balance

3. Knowledge of hypothalamic integration of caloric deposits and fuel intake--anatomic and physiologic

4. Knowledge of insulin resistance in obese state and possible application to pharmacologic approaches

5. Knowledge of limited beta cell replication in the diabetic patient and why the insulin resistance with obesity cannot be overcome by greater insulin production

6. Better knowledge of caloric homeostasis such as determination of caloric expenditures at different degrees of adiposity

B. PSYCHOLOGIC

1. Relationship to behavior and caloric intake and storage at all ages, particularly infancy

2. Studies into the social impact and interplay of obesity, nutrition, and economic status

3. Studies into behavior modification techniques and applicability to larger populations

4. Studies in energy expenditure, exercise patterns, and activities, and in the instigating and suppressing of emotional factors

C. EDUCATIONAL

1. Professional: Better nutrition education in medical schools; Broader and greater training programs for nutritionists and other allied health personnel; and Training of physiological psychologists.

2. Public: Education in grammar and high schools; Education to mothers directly; Better delivery system for nutritional education to all segments; Development of cadre of school teachers more trained in nutrition.

D. RESOURCES

Equipment centers, such as total body calorimeters, under water weighing, etc; Experimental animals for genetic, environmental, and nutritional studies; and National workshops for exchange of knowledge between various disciplines.

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E. THERAPEUTIC

Evaluation of dietary, behavioral, and pharmacologic approaches; What is best diet? Role of anorexigenic agents; Role of surgical procedures; Role of group vs. individual therapy; Need to initiate therapy early in life; Need for setting up national miminal guidelines to prevent irrational and potentially dangerous therapy from being used by some "obesity experts," professional and non-professional; and the Need for setting up standards as to who should be treated and how vigorously (cost-risk-benefit ratios).

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IV. SUMMARY OF THE WORKSHOP ON
DIABETIC RETINOPATHY

A. PRESENT STATUS-RESEARCH

Diabetic retinopathy is presently the second and will soon become the first most common cause of blindness in the United States.

The basic pathology of the lesion is the occurrence of out-pocketings or "microaneurysms" in the retinal capillaries which is followed by intraretinal hemorrhages, changes in the blood flow through the retina due to vascular shunts between arteries and veins, and finally new formation of vessels with resultant formation of scar tissue and hemorrhage in the fluid filling the back of the eye, the "vitreous" of the eye. These progressive pathologic changes parallel the progressive loss of vision leading finally to blindness.

A key question is whether these vascular changes are the result of separate genetic defects which affect the vessels of the eye in a diabetic patient or whether they occur as a complication of the diabetic state. Long-term studies in dogs and monkeys with experimental diabetes have now clearly demonstrated that the vascular changes are complications of the abnormal metabolism in diabetes. In addition, these studies have shown that the vascular changes in the retina of dogs are markedly diminished if the animals are carefully controlled with insulin therapy. These findings provide hope that when either the cause of diabetes is found and corrected or when a therapeutic means is devised to maintain continuously a normal blood sugar in the diabetic patient, then this complication may be prevented from occurring. Quite obviously these ultimate objectives have not been accomplished as yet, therefore the hope for the prevention of diabetic retinopathy must rest on determining the precise mechanisms which lead to these vascular changes. With this knowledge it will be mandatory to devise means of arresting the further development of retinopathy in the patient with diabetes.

Studies on the mechanism of the development of diabetic retinopathy indicate that the mural cells which surround the retinal capillaries are the first cells to be affected by the diabetic process.

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Some of these cells die, which in turn affects the pattern of blood flow in the retina, probably due to loss of vascular tone, and by some means microaneurysms form in the affected retinal capillaries. Techniques have now been developed for the isolation of fragments of capillaries from the retina of experimental animals, and the maintenance of these fragments in tissue culture has resulted in the growth and reproduction of the mural cells. Biochemical studies on the retina have demonstrated the presence of aldose reductase in the retinal tissue and the presence of sorbitol in the retina of diabetic animals. These studies are of particular importance since the enzyme aldose reductase is only activated when the blood sugar is elevated to high levels resulting in the formation of sorbitol from glucose. It has been shown that in the lens of the eye the activation of the aldose reductase system with the resultant formation of sorbitol is responsible for the formation of cataracts, which is another complication of diabetes that affects the eye. Thus, in regard to diabetic retinopathy, it will be of importance to determine the precise cellular localization of aldose reductase because, if it is present in the mural cells, it could be playing an important role in destroying these cells. Several agents are now available which will inhibit the enzyme aldose reductase.

The new formation of blood vessels which grow into the vitreous in diabetic retinopathy is the end-stage of the lesion which frequently results in total blindness. Studies on a variety of neoplasms have now demonstrated the presence of a vasoproliferation factor which stimulates the formation of new blood vessels. These neoplasms have been implanted in the eye, and no vascular proliferation occurred until the tumor cells contacted the vascular bed. These findings raise the question of whether the normal vitreous contains an inhibitor to the vasoproliferative factor and the diabetic patient either lacks the factor or else possesses too much of the proliferative factor. Studies are currently in progress.

Since the new formation of blood vessels in the eyes of the diabetic patient are of such importance in leading to blindness, technical procedures have been developed to photo-coagulate retinal blood vessels by means of light or a laser beam. It is completely unknown at the present time whether this approach will have any affect on the progression of diabetic retinopathy. In order to answer this vitally important question, the National Eye Institute has initiated an excellent controlled study of this possible means of therapy which involves 15 medical centers and 1800 patients. This is a five year study and the results will be of vital importance in determining whether photocoagulation is of value or is harmful in attempting to control the progression of diabetic retinopathy over a period of years.

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The proliferation of new blood vessels into the vitreous may result in hemorrhage into the vitreous. The assumption has been made that blood in the vitreous is harmful, therefore, the National Eye Institute is initiating another controlled clinical trial to determine whether vitrectomy soon after hemorrhage occurs has significant beneficial effect. Vitrectomy may also be of use in removal of chronic scar tissue such as in an eye thought to be irreversibly blind for a period of time.

B. PRESENT STATUS-MANPOWER

The need for research manpower in diabetic retinopathy is critical. Last year only two research fellowships were awarded for research training in this area. The number of laboratories with a significant number of full-time investigators devoting their entire efforts to this area is a total of only four to five in the entire nation.

V. SUMMARY OF THE WORKSHOP ON
GENETICS, VIRUSES, AND ANIMAL MODELS

A. GENETICS

Although a separate workshop under the auspices of the Committee on the Scope and Impact of Diabetes has dealt specifically with the hereditary transmission of diabetes in man, part of this workshop of the Committee on the Etiology and Pathology of Diabetes was devoted to genetics because of the close relationship between inheritance and virus causation, and especially because of the very close relationship of those factors in experimental animal models.

Familial clustering of diabetes was described in the ancient Hindu literature and genetic factors have been reported repetitively ever since. On the other hand, the prevalence of the disease waxes and wanes with the nutritional state of the population under study which suggests a strong additional environmental input. Furthermore, studies into diabetes inheritance in man have confusingly shown patterns in keeping with every known mode of genetic transmission. Rimoin has listed the number of genetic and chromosomal abnormalities which are associated with diabetes mellitus, and these suggest that it is not attributable to a single or even two or three defects, but rather that it is probably the result of a number of abnormalities leading to the same phenotypic expression.

The other problem in trying to make sense out of inheritance is the variability of the disease itself. It may present itself as a transient minimal glucose intolerance; or very rarely it even presents itself as normal glucose tolerance but in the presence of one or more of the specific complications in the kidney or the eye; or, on the other end of the spectrum, it may appear in a previously healthy child progressing in a week or two to death in ketoacidosis. Both ends of the spectrum appear more frequently with each other within the same families, and in these they appear more frequently than in the general population, consequently there appears to be a common inherited predisposition to both juvenile-type and maturity-onset type diabetes.

Several breakthroughs have been made in the past few years. The geneticist's best tool, the comparison of identical and fraternal twins, has shown that maturity-onset type diabetes has a very strong inherited component, being present in both twins over 90% of the time. Surprisingly, in juvenile diabetes, concordance occurs only 1/2 of the time, and, as Pyke has shown, if the nondiabetic twin does not develop diabetes within two to three years of the affected twin, he or she will probably not develop the disease. Thus, environment plays a very prominent role in juvenile type diabetes. Yet paradoxically, it is the maturity-onset type that waxes and wanes with the nutritional state of the population!

Another breakthrough has been the finding of the Danish group, as reported by Nerup, that in juvenile diabetes, certain tissue transplant antigens appear more frequently than in the general population, especially HL-A-8 and W-15. There appears to be no correlation with various transplant antigens and maturity-onset type diabetes. Next, workers both in the U.S. and abroad have found a high incidence of antibodies to other endocrine glands in relatives of juvenile diabetic patients, as well as antibodies to pancreatic islet tissue in many of the diabetic patients themselves. The current theory, therefore, is that either the genetic predisposition sensitizes the beta cells to some form of insulin, such as a virus, or that the genetic predisposition permits the insulin to initiate a reaction by which the body turns against its own beta cells, placing diabetes into the autoimmune group of diseases. Again, this sequence is applicable only to the juvenile-type of diabetes.

Other new data of significance include the characterization of certain kindreds, such as the families described by Tattersall and Fajans, in whom a maturity-onset type of diabetes is inherited in children in whom a dominant role of inheritance is compatible with the observed phenomena.

VIRUSES

Anecdotal reports of the development of juvenile diabetes after measles, mumps, and even after the common cold have appeared for decades. Also, the clustering of new cases, as occurred in the Tampa-St. Petersburg area of Florida, or Buffalo, New York, have been noted. However, not until Gamble and Taylor in England correlated newly diagnosed patients with juvenile diabetes with Coxsackie-B virus infection did the case become stronger. Also, the inflammatory-cell invasion of the islets of Langerhans in recent onset juvenile diabetes, as reported by Gepts, would be in keeping with viral infection and destruction, and possibly with subsequent autoimmune destruction to finish the job. The next major impetus came from the reports of Craighead and colleagues that

variants of the Encephalomyocarditis virus could cause diabetes in mice, and even in sub-human primates. Interestingly, only certain strains of mice were susceptible, reminiscent of the predilection of juvenile diabetes to individuals with certain types of tissue transplant antigens in man. Currently, attempts are being made in certain centers to isolate virus from patients with newly discovered diabetes.

But the problem remains, since most of these viruses affect such a large part of the population, why are most children spared from diabetes?

C. ANIMAL MODELS

The capacity to either cause a specific disease to occur in an experimental animal or else to breed animals who develop the disease spontaneously provides opportunities to medical research far beyond studies of the same or a similar disease in man. Breeding experiments can be done, animals can be sacrificed at will for analysis, and various factors such as new drugs can be tested as to effectiveness. Thus, animal models are crucial to studies of certain diseases, particularly metabolic diseases such as diabetes. Two chemical agents, alloxan, and more recently, streptozotocin, almost specifically destroy beta cells in animals, and their use has been of immense value in studies on the metabolic effect of insulin and its lack, and particularly to studies of complications such as neuropathy, nephropathy, and retinopathy. However, these agents are of limited use in studies on the beta cells themselves as related to the underlying etiology of diabetes. For this purpose, the development of animal models which spontaneously develop diabetes has been of much help. The first of these was the obese-hyperglycemic mouse which was discovered by accident in the Jackson Labs, Bar Harbor, Maine. In this animal, obesity and mild diabetes is a result of inheritance of two recessive genes, one from each parent. A single gene results in only a carrier state and neither obesity nor hyperglycemia. Coleman has shown that the strain of mouse bearing the ob/ob genes is as crucial as the genes themselves. In one strain there is obesity and hyperglycemia, but the hyperglycemia eventually disappears as a result of exuberant insulin production by extremely hyperplastic islets of Langerhans. In another strain, in which the same ob/ob genes are placed, the beta cells in the islets cannot match the challenge, and relative insulin deficiency results in a more severe hyperglycemia, ketoacidosis, and death. The difference between the strains is apparently something to do with the capacity of beta cells to divide. Other mutations bred into these two strains also result in similar types of diaetes in each, maturity-onset type in one and juvenile-type in the other.

In another experimental animal model, the spiny mouse, the lesion appears to be an inability to release insulin. In yet another, the Chinese hamster, bred over the past decade by the Upjohn Co., diabetes appears to result from at least four additive genes, the number of which when increased increases the severity of the disease. In these hamsters, unlike many of the obese experimental animals, a primary beta cell deficiency appears to be the cause. It should be emphasized that these same animals also develop a type of diabetic neuropathy, nephropathy, and retinopathy.

In one group of guinea pigs and also in a recently developed colony of rats in Canada, the inheritance of diabetes is so variable and ill-defined that an infectious agent may be the cause. Finally, in most of the experimental animals, the limitation of food intake early in life either prevents or postpones the diabetes, so again nutritional factors, as in man, play an important role.

D. NEEDS

1. Genetics

Further tissue transplant typing of specific kindreds as well as populations such as newly discovered patients with juvenile diabetes and well-defined groups such as the Pima Indians, etc. should be carried out. This is particularly true for the MLC locus at which preliminary studies show a much higher prevalence than the W-15 and HLA-8 alleles for juvenile diabetes. Thus, more sophistication into tissue type will help identify those individuals who are at greatest risk to develop juvenile-type diabetes.

Next, a central registry is mandatory in order to characterize index cases, patterns of juvenile diabetes, seasonal incidence, etc. Pooling of resources is also essential, as evidenced by the collaborative Scandinavian study reported by Nerup of Copenhagen.

Other needs are outlined in the report of the Workshop on Genetics of the Committee on the Scope and Impact of Diabetes.

2. Viruses

This area is almost open-ended because viruses may lie at the basis of many diseases: multiple sclerosis, rheumatoid arthritis, not to mention the cancers and leukemias. However, characterization of viruses which are beta cell cytotoxic requires isolation, characterization, and probably tissue culture of the beta cells to enable the study of the interactions between the viruses and the beta cells. Because of the sporadic nature of juvenile-type diabetes, the pooling of resources is

mandatory, similar to pooling of tissue-typing capacities for further study into the genetics of diabetes. Facilities, similar to the Cell Culture Repository of the National Institute of General Medical Sciences (NIGMS), for storing both sera and isolated pathogens from patients with juvenile diabetes need be set up. The Center for Disease Contol in Atlanta is a most logical location.

3. Animal models

The country possesses but one single resource for the development of experimental disease mutants, namely, the Jackson Laboratories in Bar Harbor, Maine. However, the facility is limited to mice, so possible new mutants, such as the new spontaneous diabetic rat developed by Chappell in Montreal, cannot be taken in and bred into uniform lines. The Chinese Hamster colony of Upjohn has been, and will continue to be, an excellent resource for this animal model, but how long the Upjohn Company will continue to support the colony at approximately $300,000 per year (direct) cannot be ascertained. Thus, central facilities should be set up and supported for the maintenance of these strains and mutants.

An alternative, still in the experimental stage, is the isolation of fertile ova from these animals, and their storage in the frozen state for later implantation into uteri months or years hence. This would prevent the loss of certain animals, such as the Zucker "fatty" rat, which almost was lost two years ago.

VI. SUMMARY OF THE WORKSHOP ON
ISLET TRANSPLANTATION AND ARTIFICIAL BETA CELL

A. INTRODUCTION

The beta cells of the pancreas have the remarkable ability of being able to detect the concentration of sugar in the blood, to respond immediately, and to release the appropriate amount of insulin in order to maintain the blood sugar in a narrow, normal range. In the diabetic patient, these cells are apparently defective with a resultant lack of control of the blood sugar. Our present form of insulin therapy does not provide moment to moment regulation of the blood sugar, and it is believed that some of the complications of diabetes (blindness, renal failure, and neuropathy) occur because of the inability to maintain continuous normoglycemia. Some feel the accelerated atherosclerosis is also augmented by this abnormal metabolism. Thus, work is in progress to attempt to develop two new forms of therapy which would provide moment to moment control of the blood sugar and hopefully would prevent the vascular and neurologic complications of diabetes. These new approaches are as follows:

1. Replace the defective beta cells with normal islet cells by transplantation.

2. Develop an implantable artificial beta cell.

1. TRANSPLANTATION

a. Pancreas Transplants

From December 17, 1966 to July 1975 a total of 46 pancreas transplants in diabetic patients have been reported. A variety of surgical techniques for transplantation of the pancreas have been used which range from implanting the whole pancreas to utilizing a segment of the pancreas with or without ligation of the pancreatic duct. The best technique for pancreas transplantation remains undecided.

The experience from 1966 has clearly demonstrated that transplantation of either a segment of the pancreas or the total organ will maintain normoglycemia without additional insulin therapy.

At the present time (July, 1975) four patients have pancreas transplants which are still functioning 10, 12, 22, and 37 months after transplantation. It is unknown whether the progression of the complications of diabetes has been altered by these transplants.

The major future problems with respect to human pancreas transplantation are as follows: to establish a standardized surgical technique; to obtain an evaluation of the potential long-term hazards to a patient receiving only a pancreas transplant since immunosuppressive agents must be used to maintain the graft; and, if further transplants are to be accomplished, a specific protocol should be established to define the status of the vascular and neurologic complications of diabetes prior to and following transplantation.

Since vascularized pancreatic grafts in diabetic patients have been shown to be functional and to maintain normoglycemia, it is recommended than an Advisory Committee be established to review the status of this approach and to evaluate the possibility of conducting a limited, carefully-controlled, clinical trial of pancreas transplantation.

   b. Islet Transplantation

The islets of Langerhans consist of small islands of cells throughout the pancreas, and these comprise only 2% of the total weight of the pancreas. The beta cells are found only in the islets of Langerhans. Thus, an ideal approach would be one which would permit the isolation of intact islets of Langerhans from the rest of the pancreas so that only these would be used in transplantation. This ideal has been accomplished in the experimental animal. Intact islets have been isolated from the pancreas and injected into the vascular system of the liver of diabetic rats of an inbred strain. The transplants have cured the diabetic state in these animals. Dispersed fetal and newborn pancreatic tissue injected into the peritoneal cavity of diabetic rats of an inbred strain has also produced reversion of the diabetic state to normal.

The islets are antigenic, and, when transplants are accomplished between different strains of rats (allografts), the islets will be rejected. The islet transplants between strains can be maintained by the use of immunosuppressive drugs--the same as has been accomplished with kidney transplants. There is evidence that residence in the liver may provide some protection against rejection of islet allografts. This protection is not complete, but the findings provide hope that, if the donor and recipient are matched as closely as possible and a

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protective transplant site is used, then mild immunosuppression might allow prolonged islet allograft survival. These immunologic problems and the search for protective transplant sites are extremely important problems to be pursued with respect to eventual islet transplantation in man.

Progress has been made with respect to in vitro storage of the islets prior to transplantation. Islets can be maintained in tissue culture for several days, and they then can be transplanted successfully into diabetic inbred rats. These studies need to be extended as well as those toward devising means of storing islets by cryopreservation and possibly other procedures. In addition, work is needed to attempt to induce replication of beta cells in tissue culture in order to provide supplies of cells for transplantation.

A most important question is whether the transplantation of islets in the experimental animal has any effect on vascular and neurologic complications of diabetes. It has been shown that the kidneys of diabetic rats have changes within them which are similar to early renal changes that are present in diabetic patients. Transplantation of islets in the diabetic animals has caused these early lesions to disappear. These findings in the experimental animal provide encouragement that transplantation in man may prevent the further progression of kidney complications. Investigations of the effect of islet transplantation on vascular and neurologic complications, which have been reported in certain animal models with a hereditary form of diabetes, should be pursued, as well as extending studies in animals with experimentally-induced diabetes.

The exciting and encouraging results on islet transplantation in the experimental animal have paved the way for attempting to resolve the problems that would permit successful islet transplantation in diabetic patients. The number of islets of Langerhans in the normal human pancreas is approximately 1,000,000 as compared to 1,000 in the rat. Thus, methodologic techniques need to be developed for mass isolation of normal human islets under sterile conditions. Progress has been made in this area, but there are still difficult technical problems to be overcome. Further development of procedures for storage of islets prior to transplantation and for induction of replication of islet cells in vitro must be pursued. While these technological problems are in progress, definitive protocols must be established for the evaluation of the results of islet transplantation in man with respect to the effect of the transplants not only on carbohydrate metabolism, but also on the vascular and neurologic complications of diabetes in the recipient patients.

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Human islets have already been transplanted into a small number of diabetic patients who had received a kidney transplant for end-stage diabetic nephropathy and who were, therefore, on immunosuppressive therapy. The amount of islet tissue injected represented only a small percent of the total islet tissue in the pancreas. Normoglycemia was not achieved in the patients and studies are in progress to determine whether the small amount of tissue was functional in these patients.

2. ARTIFICIAL BETA CELLS

a. Macro-Artificial Beta Cell

A large device has been developed which permits clinical investigations of the moment to moment control of blood sugar in diabetic patients, using small samples of blood collected in an indwelling venous catheter. This device contains three components: a blood glucose sensor, a computer, and a hormone delivery system. The initial studies with this instrument were accomplished in diabetic depancreatized dogs, and computer programs were developed which would permit the maintenance of normoglycemia in the animals. This system has now been used in studies in diabetic patients, and with this instrument it is possible to maintain normoglycemia for a 2-3 day interval. This system now makes it feasible to obtain basic information on the patterns of glycemia in diabetic patients; to determine how these are affected by diet, exercise, fasting, and emotional distress; to determine the insulin and possibly other hormonal requirements that need to be injected continuously to maintain normoglycemia; and to determine the rate and pattern of hormonal injection that will be required to maintain carbohydrate metabolism during the normal daily activity of a diabetic patient. Further clinical studies are needed with this device to define the functional hormonal defects in diabetic patients and to provide the basic information that will be required in developing a miniaturized, implantable, artificial beta cell. At the present time this macro version of an artificial beta cell is being used for clinical investigations of diabetes in two laboratories in Canada, one in Germany, one in Australia, and one in Tokyo. There are none in use in the United States at this time.

b. Micro-Artificial Beta Cell

The ultimate objective of creating an artificial beta cell is to develop an implantable device that will provide moment to moment regulation of the blood sugar of the diabetic patient. The three components are the same as for the macro version of the artificial beta cell: a sensor for blood glucose or tissue glucose, a mini computer to interpret the signal from the sensor and to control the third part of the system, which is a mini-pump that will accurately inject the appropriate amount of hormone.

The glucose sensor is one of the important and key elements in the development of an implantable artificial beta cell. Two types of sensors have been miniaturized and are currently being studied in the laboratory and

in experimental animals. The problems to be resolved are: to determine the long-term stability of the sensors with respect to interference with their function by proteins or trace metals depositing on the sensor; to establish whether tissue fluid or the blood stream should be the appropriate site to monitor the level of blood sugar; and to search for artificial membranes which will be compatible with human tissue and not provoke intense scar formation.

Bessman has developed an ingenious ultra-micro pump. The pump consists of two piezo-electric discs facing each other on a plastic ring. When a positive or negative voltage is applied to them, the tiny discs move toward or away from each other. This movement creates the propelling force to pump fluid out of the chamber through a micro-valve system. The size of the unit is approximately as large as a half-dollar.

Miniaturization of the computer system linking the glucose sensor with the pump is in progress. This aspect of the problem would be the least difficult with respect to miniaturization, however the type of programing of the computer will require information obtained from studies on diabetic patients using the macro-artificial beta cell.

c. Artificial Prosthesis Containing Islet Cells

A unique transplantation system is being studied which contains artificial capillaries connected to the vascular system with islet cells that are living on the outer surfaces of these capillaries. The artificial capillaries permit the passage of nutrients from the blood to the islet cells and the passage of insulin from the cells into the blood. The intriguing feature of this approach is that the artificial capillaries would exclude the killer cells of the blood stream and protect the islets from immunologic rejection. This model does work well when the artificial capillaries are perfused with tissue culture medium, and studies are in progress to attempt to link the capillaries to the vascular system of diabetic animals. The approach of using an artificial prosthesis containing functioning islet cells that would be protected from immune rejection needs further exploration.

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VII. SUMMARY OF THE WORKSHOP ON
INSULIN PRODUCTION AND METABOLIC EFFECTS

A. INSULIN AND GLUCAGON SECRETION

The establishment of the cause and ultimate cure of diabetes rests upon an understanding of the basic mechanisms of hormone secretion by the islet cells. In the last several years there have been remarkable advances in understanding the mechanism of islet cell secretion which has provided insight into these basic mechanisms for the islet cells in particular, but it has also provided basic information for understanding the function of cells in general. For example, studies on insulin formation by beta cells demonstrated a precursor of insulin -- proinsulin. The structure of proinsulin was determined and it was found that a portion of the molecule, called the C-peptide, was removed and the molecule was therefore converted to insulin. These studies provided insight not only into insulin formation but also into protein formation by many different types of cells. Dr. Dorothy Hodgkin in England received the Nobel prize for her remarkable studies on the crystalline structure of an insulin molecule. This investigation demonstrated how the building blocks (amino acids) of insulin were arranged in the molecule, and it thus opened the way for attempting to understand the molecular organization that was required for the action of insulin. Quite obviously this information transcended the field of diabetes and affected many, many other areas in basic science. Another example was the demonstration that the beta cell contains contractile elements which guide and propel the packets of insulin to the cell surface following glucose stimulation. This finding has provided insight into the mechanism of secretion by other endocrine cells, and it also is related to the mechanism of transport of macromolecules in nerve fibers. Thus, basic advances in one area, such as in diabetes, extend beyond the particular field and affect others. Likewise, basic advances in other disciplines are also applicable to understanding the structure and function of islet cells. The ultimate objective of determining the normal mechanism for the formation, storage, and release of insulin and glucagon from the islet cells is to use this information in searching for defects in these events in diabetic individuals. When the defects are established, then means can be obtained for either correcting or bypassing these abnormalities, thus providing the ultimate cure for diabetes mellitus in man.

B. INSULIN FORMATION

The insulin molecule consists of two chains of amino acids called the A & B chains, which are held together by bridges of sulfur atoms. Until 1967, it had been assumed that the A chain and B chain were made independently in the beta cells and then recombined to form insulin. The brilliant work of Dr. Steiner, at the University of Chicago, demonstrated the existence of a precursor for insulin which was a single chain of amino acids and was called proinsulin. In further studies, he showed that approximately thirty of these amino acids could be specifically cleaved out of this chain, leaving the A and B chains as a molecule of insulin. The thirty amino acids which were cleaved from proinsulin were called C-peptide. The composition of the C-peptide in different species of animals has been determined, and it was shown that the C-peptide was different for each species. This finding was of tremendous significance because it now made it possible to use immunologic techniques for the specific identification and measurement of human C-peptide. Consequently, one could determine the capacity of the islets in a diabetic patient to secrete endogenous insulin even though the patient was being treated exogenously with beef or pork insulin.

The sequence of events leading to the formation of insulin in the living beta cell is as follows: glucose stimulates the new formation of the precursor of insulin - proinsulin; proinsulin is conveyed to a specific area of the cell where the C-peptide is split off leaving the insulin molecule; the insulin molecule and the C-peptide are packaged and inserted into membranous sacs which are then stored as thousands of tiny packets of insulin in the beta cell. There are several basic problems which remain unresolved in insulin formation. For example, it is unknown how glucose informs the beta cell to produce more and new proinsulin. Determining how this simple signal -- glucose -- initiates the biochemical synthesis of insulin will provide basic information that may well be of importance in detecting a defect in the beta cells of certain diabetic patients, and it will also be of tremendous importance in understanding the mechanism of protein production in other cells. Large quantities of beta cells are needed for such studies, therefore investigations are in progress to obtain beta cell lines which can be grown indefinitely in tissue culture.

Until a cure is found for diabetes, our nation and the population of the world will be dependent upon a continued supply of insulin for the therapy of the diabetic subject. With the increasing population, there is concern as to whether adequate supplies of insulin can be obtained from beef and pig (and sheep) pancreases. Thus, continued investigations are needed to attempt to make insulin in the laboratory by chemical means. Small amounts of insulin have been synthesized chemically, but further work is needed since the yield is very low and the process at present is prohibitively expensive. Another approach that may be feasible is to use lower organisms such as bacteria to produce insulin. This would be accomplished by devising means of isolating the specific gene that is responsible for insulin formation in the beta cell and then to incorporate this genetic material

into bacteria so that these organisms would produce insulin. Therefore, basic information that is being obtained with respect to insulin formation can be used in attempting to avoid a potential crisis in the future with respect to the world supply of insulin for diabetic subjects.

C.   INSULIN SECRETION

Clinical studies have now demonstrated that the beta cells of certain diabetic individuals are sluggish in their responsiveness to glucose stimulation and that they do not immediately release enough insulin at the proper time to maintain a normal blood sugar. It is imperative that we understand how the normal beta cell releases insulin following glucose stimulation so that a search can be made for the defects that may be present in the beta cells of these patients.

Exciting advances have been made in this area, and it now appears that a specific receptor may be present on the membrane surface of the beta cell which recognizes and interacts with glucose. The interation of glucose and the specific receptor initiates the formation of chemical messengers which convey this information to certain compartments of the cell with the resultant release of the appropriate number of packets of stored insulin molecules into the blood stream. A simple chemical element-- calcium--appears to be one of the intracellular messengers. It appears that the messenger--calcium--may then react with a contractile protein in the beta cell causing the protein to contract and move packets of insulin to the surface of the cell where they are ejected into fluid surrounding the beta cell. The packets of insulin dissolve in the fluid and pass into the blood stream where the insulin is transported to target tissues such as muscle and fat. Further studies are needed to identify and characterize the specific receptor for glucose, to determine the precise messengers that are induced in the cell, and to determine the biochemical events that lead to the release of insulin, because a defect could be present in any one of these steps in a diabetic subject. Experimentally, it has been shown in the spiny mouse, which has a hereditary form of diabetes, that the beta cells are deficient in the contractile protein responsible for the movement of the packets of insulin to the cell surface.

The function of the beta cells is also affected by the autonomic nervous system--that component of the nervous system which is stimulated by emotions such as anger, anxiety, fear, etc. Adrenalin and acetylcholine, which are the chemical messengers of the autonomic nervous system, will alter the release of insulin from the beta cells ("adrenalin" here means epinephrine and norepinephrine). Adrenalin inhibits release, whereas acetylcholine stimulates release of insulin. These studies indicate that the autonomic nervous system has a modulating effect on insulin secretion, and it is possible that this system may play a role in the causation or enhancement of the severity of diabetes.

D. INSULIN SECRETION IN DIABETES

Patients with diabetes mellitus are usually divided into two types: the juvenile-onset and the maturity-onset. In classic juvenile diabetes, the onset of the disease is frequently acute with a decrease in the ability of the beta cell to respond to glucose stimulation and a resultant production of the diabetic state. Over a period of many years the beta cells become less and less responsive to glucose stimulation and finally produce little or no insulin so that the patient is dependent entirely upon insulin therapy. A major objective in the optimum therapy of such a patient would be to attempt to preserve the beta cell function and not permit it to deteriorate further.

In order to determine whether beta cell function was being retained it would be necessary to measure the amount of insulin that was being released from the pancreas of the patient even though the individual was being treated with beef insulin injections. As a result of the basic studies on insulin formation and the isolation of the C-peptide of human insulin (the by-product of endogenously-synthesized insulin) it is now possible to monitor the functional status of the patient's beta cells and determine the effects of different types of therapy on preserving this function.

In classic maturity-onset diabetes, the disease occurs slowly and insidiously over a period of years. Specific tests for the functional status of the beta cells indicate that their function is impaired and then may improve and finally it remains impaired. Clinical studies of first degree relatives of diabetic patients have shown that some of these individuals have asymptomatic diabetes with a slightly impaired beta cell function which may progress to overt diabetes several years later. Identical twins of these patients have abnormal glucose tolerance over 90% of the time. Further detailed clinical studies must be accomplished in the families of both types of diabetes in conjunction with studies on genetic markers.

The search for the basic defects in the beta cells of patients with either juvenile or maturity-onset diabetes can now be initiated by obtaining isolated islets from recent expirations. Studies are now being accomplished on normal human islets to determine whether the mechanisms of insulin secretion are the same in the human beta cells as in the rat. The normal human islets can be maintained in tissue culture for several weeks thus making it possible to accomplish a variety of studies on the same islets. Similar studies will be accomplished on islets from maturity and juvenile-onset diabetic patients in order to search for defects in the formation, storage, or release of insulin. Viral studies can be accomplished on the islets in order to determine whether a viral agent is present in the diabetic cells or to test the effect of different viruses on normal human beta cells. Thus, the basic information that is being obtained on the biochemical and morphological events in the secretion of

insulin by the normal beta cell will be used as the foundation for searching for defects in these events in the diabetic beta cell.

E. GLUCAGON SECRETION IN DIABETES

Glucagon is a hormone which in many ways is antagonistic to the action of insulin since it produces hyperglycemia and breaks down amino acids, the constituents of body proteins, whereas insulin lowers the blood sugar and helps build body proteins. Glucagon is produced by specific cells found in the islets of the pancreas and in the lining of the stomach and small intestine.

Recently Dr. Roger Unger has proposed the interesting and provocative hypothesis that a defect may also be present in the glucagon-secreting cells of diabetic subjects. In normal individuals glucose administration will suppress the release of glucagon from these cells. In the diabetic animal or diabetic human subject, the administration of glucose will not suppress the release of glucagon from the islet cells. The high level of circulating clucagon in the diabetic patient would presumably stimulate the release of glucose from the liver with resultant hyperglycemia and cause the breakdown of the proteins of the body. Evidence in support of this concept has arisen from the discovery of a new hormone called somatostatin. This hormone, somatostatin, was isolated from the hypothalamus of the brain and it was assumed that the major action of this substance was to inhibit the release of growth hormone from the pituitary. However, when somatostatin was administered to diabetic animals it was found that the agent would lower the blood sugar and lower the level of circulating glucagon. Somatostatin produced the same effect in diabetic humans.

These new and exciting findings need to be pursued further since it is possible that somatostatin could be used in conjunction with insulin in the treatment of diabetic patients. In addition, basic studies are needed on the mechanism of the action of somatostatin in causing inhibition of glucagon secretion as well as determining the effect of this agent on other endocrine cells. Recent studies have shown that somatostatin is present in islet cells. This unexpected and puzzling finding must be pursued because there may be an interaction of one type of islet cell with another and a local control over the release of insulin and glucagon from the islets.

F. INSULIN ACTION

Insulin released from the pancreatic beta cells is carried first to the liver and then to all parts of the body. Its concentration in blood is infinitesimally small, 1 part in 1 billion, and therefore its determination first depended on bioassays, and since 1959, thanks to the development of immunoassays by Rosalyn Yalow and the late Sol Berson, it has depended upon various immunologic techniques capitalizing on the capacity of protein from one species to provoke combining proteins (antibodies) to be formed in another species.

The liver is the first site of insulin action where a number of metabolic events are set in motion, such as the removal of glucose and its storage as glycogen, the metabolic combustion of some of the glucose for fuel for the liver, and the conversion of some of it to fat. All of these, and others, are the result of alterations in the protein machinery inside the liver cell. The liver also is the most important site for insulin degradation, and approximately 1/2 the insulin passing through the liver is taken up and degraded. It is this active process that gives insulin in blood such a short 1/2-life, approximating 5 - 10 minutes, and it is this short 1/2-life that permits small modulations in insulin concentration to play such an active role in controlling total body fuel metabolism.

G. INSULIN - MEMBRANE INTERACTIONS

The search for an understanding of how insulin works on cells has been a most important endeavor because the knowledge of the mechanism can lead to methods whereby it can be amplified, and therefore, to the possibility of a corrective therapeutic approach to the patient with moderate insulin deficiency. Originally it was thought that insulin altered the enzymatic apparatus inside cells. However, Levine and Goldstein in 1950 showed that a most important role of insulin was to permit entry of glucose into certain cells, particularly muscle. Subsequently it was shown that adipose tissue likewise showed this effect. Nevertheless, many other investigators demonstrated numerous other changes inside the cell as a result of insulin action. Consequently, it is seen that insulin sets in motion a large number of cellular events, some to do with the cell wall, such as glucose entry, or potassium transport, or a change in the electric charge of the membrane, and others are involved with the synthesis and breakdown of proteins and other factors inside the cell.

These observations provoked two hypotheses, namely, one that insulin had a single effect which set a number of others in motion, or, that insulin itself had a number of effects. In the past few years several groups, notably Roth and colleagues at the National Institutes of Health, Cuatrecasas, Lockwood and colleagues at Johns Hopkins, and Crofford, Kono and colleagues at Vanderbilt, demonstrated that the initial action of insulin was to bind onto a site of the cell membrane which has very high specificity for the insulin molecule. Slight alterations in the structure of insulin prevented binding, and a number of fascinating events take place once insulin is bound, in that the capacity of another insulin molecule to bind in an adjacent locus is altered. Although complicated and still controversial, further research in this area is mandatory for the benefit of the vast majority of diabetic patients, the maturity-onset subjects, in whom insulin is only relatively deficient. Any approach toward amplification of the reaction of insulin on the cell surface is a major approach to the treatment of these subjects.

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Obese humans and experimental animals require higher concentrations of insulin to exert an effect on cells. This is not only true in regard to the muscle cell, but also liver cells, fat cells, and white cells in the circulation. A most fascinating problem is, how do the circulating white cells know how fat we are. In any case, Roth, Gorden, and colleagues have shown that white cells from obese subjects are deficient in the number of insulin receptors on their surfaces, and that is why it takes more insulin to work. Lockwood, Cuatrecasas, and the Hopkins group have suggested a normal receptor population but a subsequent diminution in the next step of insulin's action, whatever that may be. Their evidence is that other materials which bypass the insulin receptor but which work like insulin are less active in cells from obese man or animals.

H. "SECOND MESSENGER"

Once insulin binds to the cell membrane, as mentioned above, a large number of events occur, many within minutes. One of these is to stimulate the building of liver glycogen as well as inhibiting the enzymatic machinery for the breakdown of liver glycogen. The late Earl Sutherland received the Nobel Prize for demonstrating that when adrenalin reacts with a cell membrane, an enzyme is activated which causes the formation of what was then a new biological compound, cyclic adenosine monophosphate or "CAMP". CAMP in turn activated one or more enzymes which were responsible for putting phosphates onto proteins, these enzymes being called protein kinases. Thus, the rapid breakdown of glycogen to lactic acid for provision of emergency energy, a very important role of adrenalin, or the breakdown of stored fat and the release of free fatty acids into the blood for muscle energy use were all results of formation of CAMP, which was called adrenalin's "second messenger", the hormone itself being the first messenger. Sutherland also found that glucagon promoted rapid liver glycogen break-down via CAMP formation.

Since in liver, and also in adipose tissue, adrenalin and insulin work in opposite directions (and in liver, insulin is also opposed by glucagon) it was logical that insulin should decrease CAMP formation, and this it does. However, there are many effects of insulin which appear independent of CAMP. Larner and colleagues in Virginia have isolated a factor which appears after insulin is exposed to cells and which is active in promoting glycogen storage, an effect of insulin's "second message". Kono at Vanderbilt has been examining an enzyme involved in the removal of CAMP, and he has found this enzyme to be rapidly activated by insulin within minutes, another lead toward clarifying insulin's second message.

Rollo Park has raised the fascinating question as to whether insulin itself, or a part of the insulin molecule, an active fragment so to speak, might not gain entrance into the inside of the cell and thus be the second messenger.

In another approach, Benjamin and, independently, Avruch have been studying the rapid appearance of new phosphated-proteins in fat cells soon after addition of insulin, and in certain of these proteins insulin and epinephrine oppose each other. Yet at least one protein is affected by insulin and not by adrenalin, meaning insulin has a second message other than lowering CAMP. Goldberg of Minnesota as well as Cuatrecasas have examined other nucleotides and have found effects of insulin, but their physiological roles remain unclear.

I.   INSULIN'S OVERALL PHYSIOLOGY

The overall role of insulin in physiology has been the topic of much research since Banting and Best in 1921 isolated the first active preparations. Its principal role appears to be the body's signal that there is ample fuel in the blood stream. Thus, after a meal, insulin levels increase to signal tissues to remove and store the excess fuel as it is absorbed from the gut. In between meals, the lower, but finely regulated, insulin levels control the rate of release of the fuels from the stores back into the blood in order to keep the body machinery working.

This fine tuning requires two phenomena which are crucial to diabetes and its therapy. One is an accurate and rapid ability of the beta cells to respond with insulin release to changes in fuel concentrations, principally glucose. Too much or too little insulin, or delayed insulin release, results in errors in fuel concentration. If too little insulin is released, hyperglycemia or diabetes occurs, and if this condition is extreme, the result is ketoacidosis and death. If too much insulin is released, hypoglycemia occurs, causing inadequate fuel for the brain and unconsciousness, and again, if this condition is severe or prolonged, it results in disability or death. The other pheonomenon required is a rapid and accurate capacity for tissues to respond accurately to the insulin signal. As discussed, obesity blunts this response, therefore fat people need excess insulin and, if the beta cells cannot meet the challenge, diabetes ensues. There have been recently described rare subjects in whom insulin is almost ineffective in tissues. These individuals, some of whom lack fat from birth or lost it later in life (hence "lipoatrophic") and some of whom have normal fat, can tolerate thousands of units of insulin. Some have factors in their blood which negate insulin's binding to cell walls. Further study of these and what they are lacking will certainly provide major clues as to how insulin works on cells.

J.   GLUCAGON

As discussed earlier in this report, glucagon has become an important topic in diabetes research. It is in excess in people with diabetes and fails to suppress with glucose administration. Its role is to increase CAMP in liver, and therefore to oppose insulin's action and to cause the liver to form glucose both from glycogen (glycogenolysis)

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and to make glucose anew from amino acids (gluconeogenesis). Soma-tostatin (see above) has been used to inhibit glucagon release in the presence of steady levels of insulin, and a lowering of glucose occurs, meaning glucagon does have an active role in maintaining blood glucose levels. Unger has postulated that diabetes might be a bi-hormonal disease with too much alpha cell production of glucagon and too little beta cell production of insulin. This has been questioned by some studies which show minimal or no effects of added glucagon to man or experimental animals; therefore, once again, it is evident that much research needs be done.

VIII SUMMARY OF THE WORKSHOP ON
MICROANGIOPATHY AND MACROANGIOPATHY

A.   INTRODUCTION

The vascular system of the diabetic patient is a central focus for many of the complications that occur in these patients. Clinically, these vascular complications include blindness, renal failure, coronary arteriosclerosis with myocardial infarction, cerebral arteriosclerosis often with stroke, atherosclerosis of the large arterial vessels, and gangrene of the foot. The vascular pathology is divided into two major categories: 1) microangiopathy, which is an alteration of the small blood vessels (capillaries); and 2) macroangiopathy, which is an involvement of the large blood vessels of the body.

Microangiopathy is a specific vascular change that occurs only in diabetic patients and causes the failure of the kidney and the loss of sight. Macroangiopathy is simply arteriosclerosis of the large vessels, and thus it is not limited to diabetic patients, but diabetes plays a role in accelerating the development of arteriosclerosis. The discovery of insulin in 1921 provided a miraculous therapy which prevented the immediate death of certain diabetic patients, but, unfortunately, did not cure diabetes. The vascular complications, microangiopathy and macroangiopathy, are not prevented by our present means of treating diabetic patients. Thus, the research in this area is directed toward understanding how diabetes causes microangiopathy because an understanding of this mechanism may make it possible to devise therapeutic means which will correct or prevent the damage to the small blood vessels in diabetic patients and thus prevent blindness and renal failure. Similarly, research is directed toward understanding how diabetes exacerbates the development of arteriosclerosis because this information would provide clues as to why arteriosclerosis develops in the population in general and it may also provide a solid basis for preventing or halting the progress of this vascular disease. Significant and exciting advances have been made in diabetes research in each of these areas.

A.   MICROANGIOPATHY

Capillaries are a network of small blood vessels that link the arterial and venous portions of the vascular system. These tiny structures are vitally important for conveying the blood close to the cells of the body thus permitting the rapid exchange of nutrients and oxygen and the removal of waste materials from the body cells. Their structure is uniquely suited for this function since they are composed

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of a single layer of cells (endothelial cells) which are joined together
and form a hollow tube for the passage of blood through them. The
endothelial cells are in turn surrounded by a simi-rigid protein
structure which has imbedded within it another type of cell that provides
support to the wall of the capillary. The encasing protein structure is
called the basement membrane. These three simple structures (endothelial
cells, basement membrane, and supporting cell) hold the secrets as to how
and why microangiopathy occurs in diabetes mellitus.

In studying microangiopathy, the first question was whether one
could demonstrate a specific change in any one of these structural
elements of the capillaries in the eyes and kidneys of diabetic patients
with renal failure and blindness. With electron microscopy and light
microscopy, it has been shown that the basement membrane is thickened
in the capillaries of the eye and that the supporting cells of the
capillaries are decreased in number. These changes result in the
development of outpocketing, or aneurysms, of the capillaries, rupture
of these vessels with hemorrhage, and resultant partial or complete
blindness. The kidney is responsible for filtering the wastes from the
blood stream and this filtration occurs in thousands of little clusters
of capillaries called glomeruli. In diabetic patients with renal failure,
the basement membrane of the capillaries in the glomeruli is thickened
just as in the eye. This thickening leads to plugging and leakage of
the glomerular capillaries with the resultant production of renal failure.
Thus, the astounding fact is that capillary basement membrane thickening
appears to be the pathologic change that links these seemingly diverse
complications of blindness and renal failure.

Quite naturally these findings in the kidney and eye have led to an
investigation of other capillaries in the body in order to determine
whether this change was a generalized complication of diabetes. A simple
procedure was developed for examining and measuring the basement membrane
of capillaries in muscle biopsies of normal and diabetic patients. These
studies have shown that the change in the basement membrane in the
diabetic patient also occurs in skeletal muscle and very probably involves
capillaries throughout the body of the patient.

The development of this simple procedure for quantitative examina-
tion of muscle capillaries by electron microscopy has opened the way for
numerous studies on the factors which may play a role in the development
of microangiopathy in diabetes. It has now been shown that the basement
membrane of muscle capillaries of the diabetic child does not thicken
prior to puberty, but occurs after puberty. This suggests that the
hormonal changes occurring at the time of puberty may have an effect in
causing the changes in the basement membrane. The effect of sex
hormones, such as gonadotropins, needs to be studied in experimental
diabetic models. This simple biopsy procedure now makes it possible
to obtain objective evidence of the type of therapy used in the treatment
of the diabetic patient, such as "loose" versus "tight" control of

diabetes in children. The future application of transplantation and an artificial beta cell in the treatment of diabetes can also be evaluated in terms of the effect of those modes of therapy on the complications of diabetes mellitus. Studies on the capillaries of different types of animal models with diabetes must be extended since it would be extremely helpful to find a small animal model of diabetes which develops thickening of the basement membrane similar to that observed in human diabetes.

Several lines of evidence from both clinical and animal studies indicate that the development of microangiopathy is directly related to the diabetic state. In Denmark, repeated renal biopsies have been obtained on juvenile diabetic patients starting with the onset of diabetes and extending over a period of several years. The basement membrane of the glomerular capillaries were perfectly normal at the onset of diabetes and gradually thickened in the ensuing years. Similar findings on muscle capillaries of juvenile diabetic patients have been reported by one group in the United States. Experimentally, it has been shown that microangiopathy involving the eyes of diabetic dogs is much more severe in animals that had poor control of their diabetes as compared to good control of the diabetic state.

These findings are of tremendous importance with respect to the treatment of diabetic patients because they raise the question of the type of diabetic control needed in the treatment of the patient with respect to the subsequent development of vascular complications. They also provide hope that if one can pin-point the reason for the development of microangiopathy in the diabetic state, then means could be found to correct or prevent this from occurring, even though the patient would continue to have an abnormal sugar metabolism. Thus, research is now being directed toward: determining the chemical composition of the basement membrane in diabetic and non-diabetic patients; determining the normal synthetic steps in the formation of the basement membrane; determining which cell (endothelial cell or supporting cell of the capillary) is responsible for the formation of the basement membrane; determining which cell (endothelial cell or supporting cell of the capillary) is responsible for removal of the basement membrane; and determining the factors which affect the rate of synthesis and rate of removal of the basement membrane. In the past few years exciting advances have been made in these basic areas.

Biochemical studies of normal basement membrane, obtained from the kidney, have shown that it is a complex structure which contains collagen-like proteins as well as sugar-containing proteins. In the diabetic patient, the amount of basement membrane was shown to be increased, as determined biochemically, with some changes in the normal constituents of the basement membrane. An exciting technique has been developed which will now permit studies on the synthesis of the basement membrane by cells maintained in tissue culture. These cells are obtained

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from rat embryos. Techniques are now available for growing human endothelial cells in tissue culture. This technique provides an excellent means of determing whether endothelial cells are responsible for the formation of basement membrane as well as studying the effect of sugar, insulin, and other agents on the function of these cells. Techniques have become available in the past few months for obtaining cultures of the supporting cells of the capillaries of the eye and the supporting cells of the capillaries of the glomeruli of the kidney. Thus a remarkable array of new procedures have been developed which will now permit an intensive investigation of the normal pathway of basement membrane synthesis and the abnormalities of this pathway that exist in diabetes mellitus.

B. MACROANGIOPATHY

As mentioned in the first comments concerning the vascular complications of diabetes, the macroangiopathy, which literally involves all the blood vessels larger than capillaries in the body, and which, as atherosclerosis, is normally part of the aging process, is markedly accelerated in the diabetic patient, whether the patient be of the juvenile-onset or maturity-onset type. The statistics are covered in greater detail under the report of the Committee on the Scope and Impact of Diabetes of the Commission, but a few comments here are pertinent.

If the juvenile diabetic patient is fortunate to be in that small subgroup (approximately 1/5) who has minimal small blood vessel complications (microangiopathy), he or she will yet probably die prematurely of a myocardial infarction. Another grim fact, if a non-diabetic person develops a myocardial infarction, survival is 80% or better; a similar episode in a person with diabetes results in only 60% survival. And again, both in surveys of employees in large companies or else patients referred to large clinics and hospital centers, the diabetic patient . appears to have 3-6 fold the incidence of cardiovascular events at any given age as compared to the non-diabetic person.

Of much interest, both epidemiologically and from the point of view of the more basic, biochemically-oriented,scientist, diabetes in populations with little risk to develop arteriosclerosis, such as the Japanese in Japan or the Bantu and Nigerians in Africa, do not appear to develop the accelerated atherosclerosis in association with diabetes. Thus there are nutritional or other environmental inputs in addition to the metabolic disorder resulting from the diabetes itself.

The correlation between the severity of the atherosclerosis and blood glucose levels is relatively poor. This is well exemplified by the 35 yr. old who develops an acute myocardial infarction and, after recovery, is found to have definite but minimal diabetes. He might also

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come from a family, many with diabetes and others, with simply pre-
mature cardiovascular events and early death. Frequently, he and his
family may have normal levels of fats in their blood, but on the other
hand, elevations in either cholesterol or triglyceride will be more pre-
valent in his relatives than in the general population. Workers in
Seattle have shown that the elevated levels of triglycerides and of
diabetes are probably independently inherited factors, which, when
occurring in the same patient, place him at much greater risk than
either factor alone.

Obesity also plays a role in that it is correlated with both the
diabetes and the hyperlipidemia. It has been suggested that the high
insulin levels required by the obese to be effective in his or her
peripheral tissues increases insulin's effect on the liver and results
in excessive fat synthesis by the liver, which is then added to the blood
for export to the peripheral tissues. There is also evidence that the
capacity for the peripheral tissues, particularly the adipose tissue,
to remove the fat requires normal insulin activity. Thus, the peripheral
insulin resistence of the obese would also contribute to increased levels
of blood fats.

Thus, nutrition, particularly over-nutrition (the Western style of
eating), diabetes, and hyperlipidemia all interrelate and provoke
accelerated atherosclerosis. However, there are essentially no studies as
yet which attempt to dissect the relative importance of each of these in
the diabetic patient.

A standard form of diabetic therapy until recently was a moderate
reduction in carbohydrate intake and increasing proportionally the fat
intake to provide adequate calories. Extrapolating from the correlation
of high fat intake and atherosclerosis in the Western World and applying
the same hypothesis to the diabetic patient, an increase in carbohydrate
intake and a reduction of fat with a preferential intake of the more
unsaturated fats has been recommended recently as a more appropriate
diabetic diet. But again, even the studies in non-diabetic individuals
are inferential. The prospective large studies such as the Multiple
Intervention Risk Factor study of the NHLI, which are designed to deter-
mine if alterations in lipids, or smoking, or blood pressure do prospec-
tively alter cardiovascular event frequencies, exclude diabetic patients
as part of general policy because the presence of diabetes adds one more
complicating factor toward the already complex problem.

Therefore it is apparent that some carefully controlled prospective
studies are needed in diabetic populations relating diet, blood lipids,
and cardiovascular events; but these will probably have to wait until
further studies have been done in the non-diabetic population.

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C. BASIC STUDIES IN ATHEROSCLEROSIS

The basic process of formation of the atheromatous lesion itself is controversial. It occurs in areas where there are high flow rates and turbulence (bends in the arterial system). Its correlation with hypertension also supports a mechanical (or really hydraulic) component. Factors in the blood, such as platelets, also play an important role; and it has been suggested that the initial lesion is loss of the lining or endothelial cells, perhaps simply due to trauma from the high flow and stress, and this is followed by a patch of platelets which cluster over the site of the injury. Next there is some growth of the smooth muscle cells which are in the middle of the artery, and these proliferate into the area of the injury. Ross has shown in subhuman primates that the entire process may then subside, and months later, the tissue may appear normal. If the animals are made to have elevated blood cholesterol levels, fats accumulate in the lesion and, instead of regressing, they increase in size. It has been hypothesized that diabetes does likewise and creates an environment which induces the lesions to progress instead of disappearing.

Other theories suggest that the lesion itself may be due to a primary alteration in the endothelial cells leading to a tumorous type of growth. In any case, much further work needs to be done utilizing, again, tissue cultures to try to characterize each of the cells in the blood vessel wall, such as the endothelial and smooth muscle cells, to study the effects of insulin thereon, of hyperglycemia, etc.

Other aspects of the basic studies are directed to the disorders relating to the elevated levels of circulating lipids. In the perfused liver from an experimentally diabetic rat, increased levels of the various lipid-binding proteins are produced, and recent evidence suggests that some of these may be chemically different from those produced by liver from a non-diabetic animal. The chemical difference is a change in the carbohydrate bound to the protein, reminiscent of the changes noted in the vascular basement membrane associated with the microangiopathy. In other studies, amino acid alterations have also been noted.

On the other side, elevated lipids in the circulation may also result from defective uptake in peripheral tissues, and some investigators are currently studying the mechanisms whereby the circulating lipid is removed by adipose tissue and how the associated protein and cholesterol is disposed of as the neutral fat (triglyceride) is incorporated and stored in the fat cell.

The aforementioned helps to explain the atherosclerosis in the 1/5th of diabetics patients who have hyperlipidemia. But the accelerated atherosclerosis is also noted in the other 4/5ths, and studies on the metabolism of the muscle wall itself have shown differences between

normal and diabetic tissues. Again, more careful biochemical character-
ization is necessary using tissue culture techniques to study the metab-
olism of the endothelial and smooth muscle cells in normal and diabetic
tissues. Some evidence suggests that simple swelling of vascular tissue
which accompanies hyperglycemia leads to decreased oxygen consumption,
and this in turn may lead to formation of new cells.

Finally, the interrelationships between the microvascular and macro-
vascular sequelae of diabetes need be characterized. Pathological
studies of the heart have shown thickened basement membranes and deposits
of carbohydrate-rich protein, analogous to those materials deposited in
the kidney of the diabetic patient, and hearts in both diabetic animals
and man function less well than those of non-diabetic animals. In simple
terms, the heart is less pliable, and the frequent finding of slightly
abnormal non-specific electrocardiographic changes in diabetic patients
without much atherosclerosis may be a manifestation of the same phenom-
enon. Likewise, the frequent enlargement of the heart and occasional
heart failure without much antecedent history in the diabetic patient
may also result from this process, suggesting that non-vascular effects
of diabetes may also play a very significant role.

A. INTRODUCTION

The interrelationships between diabetes mellitus and the oral cavity are multiple. Diabetes clearly is associated with more severe and more prevalent periodontal disease, and, conversely, dental problems affect diabetes in at least two major areas: one related to mastication of the diabetic diet, and the other related to the effects of dental infection on diabetes control and complications.

CARIES

Although glucose concentrations in oral fluids are elevated (e.g. 5-6.3 mg/100) in diabetics as compared to normals (0.2-3 mg/100 ml) there appears to be no greater incidence of dental caries. In fact, caries are less in juvenile-onset type diabetic patients than in normals, and this phenomenon is certainly related to the decrease in sugars in the diet. Periodontal disease, however, is at least 3 times more prevalent in the diabetic than in the normal population, and this will be discussed.

B. PERIODONTAL DISEASE

The natural history of periodontal disease has been well described since its classification in the mid-1950's. It starts as a mild inflammation of the gums (gingivitis) and progresses to a deepening of the groove (sulcus) between the tooth and the gums with increased bacterial growth and formentation (periodontitis) and eventually in gross infection with much inflammation and pus and loosening and loss of teeth (pyorrhea or periodontosis). The same sequence occurs in non-diabetic individuals, but in diabetic patients it is more rapid and severe. In fact, alert dentists may frequently make the first diagnosis of diabetes in an individual particularly in the 20-40 year old age group in whom periodontal disease among individuals with diabetes is much more prevalent than in the normal population. An acute gingival abscess in a young individual is almost pathognomonic for diabetes.

Danish workers in Aarhus have shown a close correlation of periodontitis with retinopathy and nephropathy in the juvenile-onset diabetic patient, and the pathogenesis may be correlated with the elevated glucose

levels, the decreased host defense mechanisms, and perhaps a component related to microvascular abnormalities. Whether the gingival capillaries are involved in the almost ubiquitous basement membrane thickening, and what effect this process has on gingival disease, is a subject of controversy, although several investigators have shown a marked increase in basement membrane width in the diabetic patient.

The periodontitis leads to dissolution of the connective tissue (collagen) which cements the tooth to the bone, the teeth become loose, and eventually dislodged. In addition there is progressive disappearance of the bone itself, certainly related to the periodontitis but possibly also to the predisposition of the diabetic patient to develop softening of bone throughout the body (osteoporosis). Again, the dentist may be the first to diagnosis diabetes in a middle-aged subject with far advanced atrophy of bone about the teeth, particularly if there is also a "dry" or "burning" mouth.

The impact of periodontis on the person with diabetes extends far beyond the difficulties involved in mastication of food and the effect of infection of any sort on the diabetes and its complications. Periodontal care is expensive, and it is not covered by most third party payments. Intensive periodontal therapy can approach in cost several thousand dollars annually. In addition, the accelerated resorption of bones makes necessary frequent alterations in prostheses. Even if **totally** edentulous and dentifrices are in use, the changing bone structure necessitate refittings much more frequently in the diabetic patient than in the non-diabetic.

C. PATHOGENESIS

The pathogenesis of periodontitis in the diabetic patient has been little studied and is a fruitful area for research. In the non-diabetic person, the bacterial flora of the mouth has been intensively studied. The plaque surrounding the base of the tooth is a hard mass of mixed populations of organisms which literally erode into the enamel of the tooth. All of these organisms in the more severe forms of the disease, which lead to gross infection and tooth loss, ferment sugars with much lactic acid production. No studies of the flora in diabetic persons have yet been reported. These bacteria erode deeper and deeper around the base of the tooth, dissolving the bone as it progresses. Certain bacteria, such as Leptothrix falciformis, are usually always associated with destructive disease.

D. OTHER ORAL PROBLEMS

The infant of the diabetic mother has an increased incidence of congenital anomalies, particularly of the oral cavity, necessitating in many cases reconstructive surgery. Also, enamel abnormalities have been

noted in 3 - 5 year old children of diabetic mothers, a residuum of the altered uterine environment, but these have not been related to any morbidity.

E. NEEDS

1. Better studies on the natural history of periodontal disease in the diabetic patient.

2. Characterization of the bacterial flora in diabetic periodontal disease.

3. Experimental animal models to develop therapeutic approaches to the treatment of periodontal disease in the diabetic subject.

4. Basic studies applicable to both diabetic and non-diabetic individuals on plaque formation and its microbiology.

5. Manpower in Dental Research directed to the problems of the diabetic patient.

6. Educational programs in Dental Schools describing problems of the diabetic patient.

7. Educational programs in Medical Schools describing the dental problems of the diabetic patient.

8. Postgraduate educational programs for both M.D.'s, D.M.D.'s, and their respective paramedical colleagues describing the special oral problems of the diabetic patient and the mandatory close cooperation needed between the two disciplines in the management of dental problems in these patients.

X. SUMMARY OF THE WORKSHOP ON THE
PERINATAL PROBLEMS OF DIABETES

A. INTRODUCTION

Prior to the availability of insulin, a juvenile-onset type diabetic patient failed to survive more than one or two years, there-fore pregnancy was not even considered as a possible problem. With insulin therapy, survival was extended, but pregnancy was a threat to the mother and survival of the fetus was a relatively rare event. Diabetic ketoacidosis during the pregnancy almost uniformly resulted in fetal death and abortion. Maternal death also was far greater than in the non-diabetic population.

With closer surveillance of the control of the diabetes, maternal mortality has been progressively decreased so that at present it is not statistically different from that of the non-diabetic person (both approximately 0.3 - 0.4%). Survival of the offspring (in the 1930's about 30 - 40%) has progressively increased in some clinics to greater than 90%, which is a rather remarkable improvement, but it is still less than in the non-diabetic pregnancy.

B. MATERNAL-FETAL RELATIONSHIPS

The growth and development of the fetus involves a number of interactions between mother and fetus with the placenta interposed. In the first two to three months in formation of the fetus, all of the major structural components such as formation of limbs develop. Major congenital abnormalities occur at this time, such as gross de-formities of limbs, cleft palate, hare-lip, etc. This is mentioned because there is much evidence that congenital abnormalities are increased in diabetic pregnancies, and the persisting increased perina-tal mortality is mainly due to these. Why the infant of the diabetic mother (hereafter referred to as: "IDM") has increased abnormalities is being studied in several laboratories (a cleft-palate type lesion can be induced in offspring of diabetic rats).

In the mid and final trimesters of pregnancy, there is a progressive growth and maturation of various organs as the infant is prepared for survival in the outer world. The placenta is the organ which extracts nutrients and oxygen from maternal blood, delivering these via the

umbilical cord to the fetus, and, via vessels running in the opposite direction, waste products and carbon dioxide are brought to the placenta where they are returned to maternal blood for excretion via maternal kidneys and lungs. Certain fuels for the fetus, such as glucose, appear to cross the placenta as a function of maternal concentration. Thus hyperglycemia in the mother enriches fetal blood with glucose, and hypoglycemia the reverse. Other nutrients such as amino acids cross the placenta by active transport mechanisms. The fuel for the fetus is almost purely glucose, but other lesser fuels such as ketoacids, pyruvate, and lactate can be consumed by the fetus, however their roles appear to be quantitatively much less significant. Most important, protein hormones such as insulin, growth hormone, and glucagon do not cross the placenta, therefore the levels in the fetus and mother are totally independent. It is interesting that by the 2nd to 3rd month, the fetus is already generating its own insulin, glucagon, growth, and other hormones.

The hormonal environment of the pregnant female is also altered by pregnancy. Soon after fertilization, the implanted egg in the uterus produces a hormone, chorionic gonadotropin (HCG), and this prepares the ovary to produce enough female hormones to prepare her organs for continuation of the pregnancy. It is this hormone that is first detected in standard "pregnancy" tests. Later, the placenta produces a second unique hormone, placental lactogen (HPL) or chorionic somatomammotropin, and, as its name implies, it has effects which alter breast function as well as some growth hormone like effects. It has recently been shown that both HCG and HPL (the H's stand for human) are acutely altered by changing glucose levels.

The parasitic relationship between fetus and mother necessitates alterations in maternal metabolism to provide continued growth of the fetus. Thus, when the mother eats, the fetus receives a pulse of nutrients, however, when the mother is fasting, fetal fuel needs must be met and this is achieved by accelerated breakdown of maternal tissues. Insulin plays a major role in controlling this process. The precise roles of HCG and HPL in fuel metabolism have not been determined, nor have the roles of the maternal sex hormones, estrogen and progesterone, except that they aid in fetal growth and nutrition. Likewise, the roles of fetal insulin and glucagon remain to be characterized.

C. DIABETIC PREGNANCY

As mentioned, the IDM has an increased incidence of congenital anomalies (see Workgroup on Pregnancy of the Committee on Scope and Impact of Diabetes), but, until recently, the overwhelming problem has been perinatal death, either due to sudden death of the infant while still in the uterus, or else death of the newborn, mainly due to a respiratory failure secondary to immaturity of the lungs.

The IDM is rather unique. If the infant resides in a mildly diabetic mother, perhaps with diabetes only while pregnant ("gestational diabetes"), the infant is frequently overweight, with increased linear growth, and a marked increase in body fat content. The baby looks rosy-cheeked, healthy, and strong, but paradoxically is at high risk for several problems including death. The superb studies by Chez and colleagues at the National Institute of Child Health and Development in diabetic pregnant monkeys have done as much as any other studies to characterize the physiology of diabetic pregnancy.

Fetal glucose levels rise as do maternal glucose levels, thus the IDM is superfed, which explains the large body size. Also, the fetal beta cells become hyperplastic and, in contrast to the beta cells in the non-diabetic newborn, respond rapidly to glucose by a brisk insulin release. Thus, the newborn has excess insulin levels, and severe hypoglycemia occurs frequently which necessitates glucose therapy.

The major problem in the IDM, however, is the necessity to deliver prior to the sudden intrauterine death which is almost unique to diabetic pregnancy. Thus a mother may be doing relatively well, with active fetal movements, and within a day or two, fetal movements may decrease. Measurements of hormones produced specifically by the fetus, such as estriol, show decreased levels in both maternal urine and par-ticularly in maternal blood which signify fetal distress, and delivery must be induced prior to fetal death. Thus, close observation of the pregnant diabetic patient in the third trimester, particularly from the 35th or 36th week, is mandatory. Many clinics may even admit the patient at the 30th to 32nd week for closer supervision.

To prevent this sudden intrauterine death, induction of labor was initiated at the 36th to 37th week of pregnancy, however, many of these infants had inadequately matured lungs, and they died due to "hyaline membrane disease". Thus, for each diabetic pregnancy, it is necessary to be sure of the date of conception. Ultrasound techniques for measuring fetal head size have provided help in dating the conception, particularly since many diabetic women have irregular periods, and the dating of conception by history may thereby be imprecise.

The strategy of managing the pregnant diabetic patient is to allow maximal maturation of the infant with very close observation to anti-cipate the possible sudden demise of the newborn and to induce delivery prior to this tragic event. As stated, better overall statistics were obtained a decade ago by earlier delivery at the 36 - 37th week, but with, unfortunately, a high rate of neonatal death due to respiratory disease. Two developments have permitted later delivery. One is the capacity to monitor fetal distress prior to its irreversibility by both closer patient supervision and by following maternal estriol metabolism.

Other tests have been devised, such as the oxytocin stress test, which assays fetal well-being. These tests have permitted prolonging the pregnancy to permit more fetal maturation by providing confidence that all is going relatively well. The other development is the capacity to monitor the maturation of the fetal lungs by measuring the concentration in the amniotic fluid, obtained by a simple needle aspiration through the mother's lower abdomen, of a certain fatty material, lecithin, which appears in the amniotic fluid from the fetal lungs. Another fat, sphingo-myelin is measured as a reference. The higher the L/S ratio, the more mature the fetal lung. This ratio is either measured directly chemically or crudely by shaking to form foam. The more mature the lung, the more apt the obstetrician is to go ahead and deliver.

There is some evidence, however, that maternal diabetes alters the L/S ratio in a way which may give false evidence of adequate lung maturity. In non-diabetic pregnancy, a ratio of greater than 2 results in a newborn who has fully mature lungs and respiratory distress almost never occurs. In the IDM, ratios greater than 2 can be associated with respiratory difficulty, therefore other parameters must be studied as well as the collection of more clinical data to characterize what level in the IDM signifies adequate maturity.

A third and other very significant development has derived from the neonatologists capacity of caring for the newborn, particularly using devices for assisting respiration.

In spite of all of the developments, the IDM has still treble the mortality of the infant of the non-diabetic mother. Much of this is due to congenital abnormalities dating from the first trimester. Other problems such as hypocalcemia, hypoglycemia (already discussed), hyperbilirubinemia, and an unexplained type of heart failure occur more frequently in the IDM. In the infant of the gestational diabetic patient these also occur to a greater degree than they do in the non-diabetic pregnancy, but not to the same incidence as in the insulin-treated patient.

D. OTHER PROBLEMS IN DIABETIC PREGNANCY

The previous discussion is directed at the offspring and its viability, but the pregnant diabetic herself is also at increased risk for a number of other factors. Six patients at the Joslin Clinic died of myocardial infarction, three in the first trimester and three at delivery. Thus severe coronary artery disease is a contraindication, although 1 patient was recently carried successfully through term after coronary artery surgery in the first trimester.

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Diabetic retinopathy can be markedly exacerbated and severe vitreous hemorrhage is an indication for interruption by abortion. Thus, retinopathy is an indication for contraception. Occasional patients may experience improvement during pregnancy. The diabetic pregnant female is also at greater risk to develop infection, particularly of the urinary tract. The worse the complications are in the mother, the smaller the infant and the more frequent the intrauterine deaths and other abnormalities.

E. CONTRACEPTION AND DIABETES

The exacerbation of diabetes by pregnancy as manifested by increased insulin requirements of the diabetic patient already on insulin or by the appearance of abnormal carbohydrate metabolism in the previously non-diabetic (gestational diabetes) alerted investigators to study carefully the effects of oral contraceptive agents on glucose tolerance. Early reports were markedly disparate, with some suggesting a strongly diabetogenic role of the pills and possibly even irreversibility of the diabetes after cessation. Other studies have shown a significant but small decrease in glucose tolerance which was completely reversible.

A large British study of 40,000 females demonstrated a prevalence of 0.17 for diabetes in females taking the pill, 0.10 in those who stopped taking the pill, and 0.19 in those who have not taken the pill. None of the differences are significant. Normal females placed on oral contraceptives may have no significant alteration in glucose levels after a glucose load, but do so by having increased insulin concentrations. Thus, in the individual with a diabetic predisposition, a worsening in tolerance may occur, and this may necessitate therapy by diet, or, occasionally, by oral agent or insulin. It is obvious that the physician must weigh the minimal sequelae of advising use of contraceptive steroids against other means of contraception, surgical sterilization, or the problems of an anticipated pregnancy. Thus broad policies cannot be made, and the mode of therapy needs to be applied to each individual case.

F. NEEDS

1. Clarification of the impact of pregnancy on the diabetic female, such as why the frequently accelerated retinopathy?

2. Studies into the increased congenital malformations of the infant of the diabetic mother.

3. Studies on the effects of therapy of different types and degrees during pregnancy. For example, glucose control, diuretic agents, need for early hospitalization.

4. Studies of indices of fetal maturation, such lecithin/sphingo-myelin ratio and other tests, either clinical or aminiotic fluid.

5. Basic studies on the metabolism of normal and diabetic pregnancy to characterize further the altered metabolic patterns and anatomic changes of the infant of the diabetic mother.

6. Training of personnel, professional and otherwise, who have expertise in high risk pregnancies such as diabetes and in the special neonatal care required by the infant of the diabetic mother.

7. Studies of the effects of contraceptive steroids on diabetes and its macro- and microvascular complications.

XI.   PAPERS PRESENTED TO VARIOUS WORKGROUPS
OF THE
COMMITTEE ON THE ETIOLOGY AND PATHOLOGY OF DIABETES

PREFACE

The following papers and summaries are working papers which were written for, or generated by, various Workgroups of the Committee on the Etiology and Pathology of Diabetes. The purpose of these papers has been to survey the present state of knowledge in the areas of concern so that a properly informed assessment of needs could be developed. As such they are not, and were not intended to be, "learned papers" of the type appropriate for scientific journal publication. They are working documents which have been of extreme assistance to the Committee in fulfilling its purpose, and they are included here as background support for the foregoing Workgroup Summaries.

The reader is also referred to the Report of the Committee on the Scope and Impact of Diabetes for additional information on related subjects.

RESEARCH INTERESTS REGARDING INSULIN

William B. Benjamin, M.D.

For insulin-cell membrane interactions to produce diverse effects on intracellular metabolism both qualitative and quantitative nature of membrane interactions must be conveyed to appropriate effector systems. Protein kinases are particularly important in these information transfer systems, and cyclic AMP specifically activates several of these enzymes. However, only some of insulin's many metabolic effects can be explained by insulin's modulation of the levels or effects of cyclic AMP. Although insulin may affect both adenylate cyclase and phosphodiesterase activities, there is a dissociation between at least some of insulin's actions and the intracellular levels or effects of cyclic AMP.

These and more recent observations suggest that an insulin-independent, cyclic AMP-independent protein kinase system may link the insulin-membrane receptor complex to some biochemical responses to insulin. The studies to be described imply such a mechanism of insulin action on fat cell protein phosphorylation.

Endogenous and hormone-induced protein (polypeptide) phosphorylations were studied in isolated rat fat cells, in fat pads, and in subcellular fractions obtained from fat tissue under different physiological conditions. Insulin (25-100 µU/ml) increased the incorporation of ^{32}p into 2 proteins: insulin-phosphorylated proteins (IPP 140 and IPP 50; $\sim$ 140,000 and 50,000 daltons, respectively). Epinephrine ($10^{-7}M - 10^{-6}M$) increased the incorporation of ^{32}p into another protein: epinephrine-phosphorylated protein (EPP 60-65; $\sim$ 60-65,000 daltons). Endogenous IPP 140 phosphorylation in fat cells obtained from fasted and refed rats was similar to that of insulin in normal cells.

Studies of insulin and epinephrine interactions showed that insulin increased IPP 140 phosphorylation even in the presence of epinephrine or lithium (25 mM x $10^{-3}M$). Dibutyryl cyclic AMP (5 x $10^{-4}M$) markedly stimulated EPP 60-65 phosphorylation, but neither epinephrine ($10^{-7}M - 10^{-6}M$) nor dibutyryl cyclic AMP reproduced insulin's phosphorylation of IPP 140. Lithium inhibited both endogenous and epinephrine-stimulated EPP 60-65 phosphorylation, but did not inhibit that induced by dibutyryl cyclic AMP. These findings suggest that insulin stimulated a specific, cyclic AMP-independent protein kinase for IPP 140 phosphorylation.

Cell-free extracts from insulin-treated fat tissue catalyzed the specific transfer of ^{32}p from ATP to IPP 140 more rapidly than control extracts. No differences in the total receptor protein or total protein kinase activity using $[\gamma\text{-}^{32}p]$ ATP were noted between insulin-treated and control preparations. These findings suggest that IPP 140 may be either (a) an insulin-sensitive protein kinase (phosphortransferase), or (b) a protein whose function is regulated by an insulin-sensitive protein kinase or phosphatase.

The experiments described will increase the understanding of the relationship of insulin stimulated protein phosphorylations to normal physiology. These findings will describe unique physiological effects of insulin, that which may be involved in the etiology of human disease, i.e. diabetes mellitus.

The next 5 years will witness the unravelling of the intra-cellular insulin mediated independent circuits from those insulin pathways which do interdigitate with other hormone mediated circuits. I expect that we will find evidence for both acquired and genetic impairments in some components of these pathways.

PUBLISHED PAPERS ON THIS SUBJECT

1. William B. Benjamin and Irwin Singer. Effects of Insulin on the Phosphorylation of Adipose Tissue Protein. Biochem. Biophys. Acta. (1974) 351, 28-41.

2. William B. Benjamin, Susan T. Fish and Irwin Singer. Insulin-Induced Adenosine 3':5'-Cyclic Monophosphate Independent Phosphorylation of Fat Cell Protein: Effect of Starving and Refeeding. Biochem. Soc. Trans. (1974) 2, 920-922.

3. William B. Benjamin, Irwin Singer, and Susan T. Fish. Actions of Insulin, Epinephrine and Dibutyryl cyclic AMP on fat cell protein phosphorylation: Cyclic AMP-dependent and cyclic AMP-independent mechanisms. Biochem. (1975) in press.

INSULIN AND SECOND MESSENGERS

John Fain, Ph.D.

It has long been attractive to postulate that insulin interacts with receptors in the membrane and that this results in the release of an intracellular second messenger. Such compounds are known to mediate the intracellular effects of many hormones. The first known example was the catecholamines and glucagon which act to catalyze the formation of cyclic AMP via adenyl cyclase which is located in the plasma membrane. The possibility that insulin might have its own unique second messenger has been attractive but is yet to be established. The work of J. Larner and associates has provided some evidence that a compound "X" accumulates in cells exposed to insulin which might mediate some or all of the effects of insulin on glucogen synthase.

Whether there is a necessity for a unique intracellular messenger to transmit the effects of insulin within cells remains to be established. What is becoming clear is that insulin affects the activity of many diverse metabolic processes in target cells and many of these effects are clearly separate. That is effect 2 is not secondary to effect 1. The levels of many compounds may change in cells exposed to insulin. This is certainly true of cyclic AMP and cyclic GMP.

The work of the Nashville group of Earl Sutherland first demonstrated that insulin could lower cyclic AMP. It is well accepted that glucose transport is not regulated by cyclic AMP with regard to stimulation by insulin. Whether any of the metabolic effects of insulin are secondary to a drop in cyclic AMP is not clear at the moment. The mechanism by which insulin lowers cyclic AMP appears to be by elevation of cyclic AMP phosphodiesterase activity. The work reviewed elsewhere by C. R. Park covers our current knowledge of this insulin-sensitive enzyme.

Our work suggests that insulin lowers lipolysis by a mechanism not involving cyclic AMP. There are other types of anti-lipolytic agents such as prostaglandins, nicotinic acid and adenosine which primarily lower cyclic AMP. However in order for insulin to inhibit lipolysis cyclic AMP must be at fairly low levels.

Nelson Goldberg and associates first showed elevations of cyclic GMP in fibroblasts by insulin. Our own work has further demonstrated that insulin can markedly elevate cyclic GMP accumulation in fat or liver cells. The effect of insulin is maximal at 2 to 4 minutes. However it remains to be demonstrated what this rise in cyclic GMP

means. Other agents which either have no known effect on processes affected by insulin in liver and fat cells and agents which have effects opposite to those of insulin also elevate cyclic GMP.

It is known that guanyl cyclase is activated by calcium and that a rise in intracellular free calcium is associated with rises in cyclic GMP. This raises the possibility that the rise in cyclic GMP due to insulin may reflect effects of insulin on calcium. There are ample published data to support the notion that insulin affects calcium dynamics in a variety of cells. The relationship of these changes to any of the known effects of insulin is unclear at the moment. There are probably interactions both at the level of formation and of action between calcium and both cyclic GMP and AMP.

RECOMMENDATIONS

Research on the mode of insulin action should be expanded for the following reasons:

1. There are good systems in which insulin action can be examined.

2. There are a wealth of new techniques from membrane biologists, cyclic nucleotide research and molecular biology which could be applied to the problem.

3. Understanding of the mode of insulin action should aid the clinical treatment of diabetes and its detection for the following reasons:

   (1) Such studies would lead to substitutes for insulin which are more effective and less toxic than the known oral agents.

   (2) While insulin has been available for 50 years it is clear that the life expectancy of the diabetic is not normal. Particularly distressing are the ocular, renal and cardiovascular side effects of hyperglycemia.

   (3) If we knew how insulin works we might be able to prevent diabetes by appropriate treatment of obese individuals. Obesity is the one condition which clearly causes an impairment of insulin action by increasing the amount of insulin required to clear a given amount of glucose.

INSULIN SECRETION IN PATIENTS WITH
ASYMPTOMATIC DIABETES

STEFAN S. FAJANS, M.D.

Insulin secretion as evaluated by insulin responses to orally or intravenously administered glucose or amino acids, were presented for groups of patients of various ages (9-17, 18-25, 26-35, 36-45 years) at diagnosis. Results were presented of cross-sectional studies as well as of prospective or longitudinal studies in patients who have been treated either with diet or diet and sulfonylurea agents for as long as 22 years (mean approximately ten years) after diagnosis.

The findings presented can be summarized as follows:

1. Although latent diabetes may progress to overt, insulin-requiring diabetes in some children, adolescents, and young adults, in 80% of young patients studied, it does not, nor does glucose intolerance necessarily advance in severity over periods of up to 22 years. In many of these patients, asymptomatic diabetes might have remained undiscovered if they had not been tested as first-degree relatives of diabetic patients.

2. In 90% of latent diabetic patients under age 25 years at diagnosis, mean insulin responses to glucose are delayed and subnormal but the insulin responses may not deteriorate over periods of up to 12 years.

3. The slow progression to insulin-requiring diabetes in some, or lack of evident progression of latent diabetes in many children, adolescents, and young adults, suggests that early detection should allow time for the institution of possible prophylactic procedures which would be more effective than those presently available, and that might arrest or reverse abnormalities of insulin secretion and glucose intolerance.

4. Although most of our latent diabetic patients have a significantly delayed increment in plasma insulin in response to glucose, the magnitude of individual insulin responses to glucose encompasses a wide spectrum. At one extreme, including the majority of patients studied, greatly decreased insulin responses appear to be the determinant, at least in part, of abnormal carbohydrate tolerance. On follow-up with therapy, the insulin responses were greater and glucose levels were lower. At the other extreme were patients with glucose intolerance with insulin responses which

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were supernormal (nonobese subjects). On follow-up with therapy their insulin responses decreased toward or to normal and carbohydrate tolerance improved. This suggests that in these latter patients, hyperinsulinemia is secondary or compensatory to factors which cause glucose intolerance.

5. The demonstration of heterogeneity of insulin responses to glucose among nonobese patients with latent diabetes supports the view that so-called "idiopathic" diabetes mellitus includes more than one disorder associated with hyperglycemia.

6. Progression to insulin-requiring diabetes (some to ketosis-prone type) occurred only in individuals with insulin responses that were delayed and lower than the mean responses of the control subjects. (None whose insulin responses exceeded this mean have decompensated.) Such an insulin response appears to be a more reliable prognostic indicator of decompensation to insulin-requiring diabetes at a later date than the degree of abnormality of carbohydrate intolerance.

Recommendations for further research on "Insulin Secretion in Latent Diabetes":

1. Insulin secretion should be studied more extensively in patients with asymptomatic or latent diabetes who can be categorized in a variety of ways:

    (a) Belonging to different age groups – young to middle age.

    (b) Different ethnic groups.

    (c) Recruited in different ways, i.e. strong family history, minor symptomatology, etc.

2. Such groups should be studied cross-sectionally with respect to insulin secretory patterns.

3. These groups should be studied longitudinally or prospectively, with proper controls as follows:

    (a) untreated;

    (b) diet treated;

    (c) oral agents;

    (d) insulin treated

    Such studies are necessary to learn more of the natural history of untreated and treated carbohydrate intolerance or diabetes in

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young people. These may be the same individuals who have maturity-onset type of diabetes in middle age or later with complications.

4. Heterogeneity of insulin responses to various nutrients, as found by various investigators, should be confirmed.

5. In patients with supernormal insulin responses one should look for abnormalities of structure in the insulin molecule.

6. In patients with supernormal insulin responses one should look for defects in peripheral receptor binding of insulin.

7. The rate of development of complications of diabetes in these patients should be ascertained.

8. Genetic differences between various groups of individuals with various types of insulin responses should be ascertained.

9. Special studies, such as histocompatibility type and fibroblast studies, should be encouraged.

10. The prognostic implications of insulin responses to glucose in terms of development of insulin-requiring diabetes and complications of diabetes should be ascertained.

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MEMBRANE INTERACTIONS IN STIMULUS RECOGNITION
Norbert Freinkel, M.D.

A. Scientific Presentation

A distinct metabolic pattern appears to supervene when a tissue is transformed from the "resting" to the "working" state. From the mid-1950's to the mid-1960's, we utilized the thyroid and stimulation with pituitary-thyrotropin (TSH) to characterize this pattern. We showed that exposure to TSH elicits in thyroid tissue: a) a rise in oxygen consumption (even in the absence of exogenous nutrients); b) a mobilization of endogenous substrates (cf. glycogenolysis; lipolysis); c) a rise in intracellular inorganic orthophosphate (P_{in}); d) an heightened turnover of certain phospholipids, especially the phosphoinositides; and an enhanced assimilation of exogenous nutrients, particularly glucose. Others demonstrated that TSH also activates the hexose monophosphate pathway, adenylcyclase, and the flux of certain cations (i.e. Na+; Ca++). We early stressed that this pattern did not appear to be unique for thyroid but that it simulated many of the events which have been observed but less well documented, during studies of the transition from "rest" to "work" in other tissues (e.g. secretory stimulation in the adenobypophysis, the exocrine pancreas, or salivary glands; induction of mitosis and/or extrusion of immunoglobulins by lymphocytes; aggregation of platelets; phagocytosis by polymorphonuclear leukocytes; excitation of neural tissue etc.) More recently, the integrated pattern of response in secretory tissues has been called "stimulus-secretion coupling" and a voluminous literature has emerged. However, the precise temporal sequence of events has not been established for any system. In the least, three sequential components may be delineated: 1) recognition of the specific stimulus by the responsive tissue; i.e. the earliest membrane perturbations which are "triggered" by the interaction between the stimulus for "work" and recognition sites at the cell surface; 2) propagation of the signal; i.e. the mechanism by which the signal is transduced, amplified and/or modulated to recruit the necessary intracellular resources; and c) performance of the specific "work", i.e. the coordination of cellular processes by which the "work" is performed (which in the case of secretory structures consists of extruding secretory products).

Although it is easy to recognize deficient "work", it has been difficult to pinpoint the underlying faulty or limiting step in the integrated sequence. Pathyphysiological dissection has been hampered by the lack of biochemical probes for monitoring the discrete components preceding the final "work" response. Today, I should like to summarize some of our recent efforts to develop such a probe for the early events in stimulus recognition by pancreatic islets. Our work with islets has been motivated by the fact that this is the only tissue in which normal nutri-

ents (e.g. glucose, amino acids etc.) can act as stimulatory signals and by the growing appreciation that defective stimulus recognition may underlie many forms of diabetes mellitus. Available technologies render islets admirably suited for attempts to dissect the component events in "stimulus-secretion coupling": Islets can be isolated so that relatively specific structures can be studied in vitro: perifusion can be instituted so that the ambient stimulus (e.g. glucose, amino acids etc.) and the final expression of "work" (i.e. insulin secretion) can be monitored on a moment-to-moment basis; and the islets can be removed from the perifusion system at any instant in time so that intracellular realignments can be correlated with ongoing "stimulation" and "secretion".

For our test system, we have extrapolated from our earlier finding that intracellular P_{in} is increased in thyroid tissue during the induction of "work" with TSH. Accordingly, we have isolated rat pancreatic islets by collagenase digestion and prelabeled these by incubation with orthophosphate ^{32}P. Following appropriate washings, such islets have been perifused with saline media containing 0 or 0.5 mg per ml glucose and then with 3.0 mg per ml. We have found that the 3.0 mg per ml glucose elicits an almost immediate transient and self-limited heightened efflux of orthophosphate-^{32}P which can be accounted for almost entirely by the release of intracellular stores of orthophosphate-^{32}P. The release ("the phosphate flush") conforms to a packet-pulse, and its magnitude displays dose-response relationship to the ambient concentration of glucose with a threshold between 0.5 and 1.0 mg per ml and a km at somewhat less than 1.5 mg per ml glucose. The phenomenon can be reduplicated by other sugars (D-mannose) known to stimulate insulin release but not by sugars which do not affect insulin secretion (D-galactose; D-fructose; i-inositol, L-glucose). The "phosphate flush" is not restricted to sugars. It can also be elicited by nutrient insulin secretagogues such as L-leucine or the b(-) isomer of the non-metabolizable leucine analogue 2-aminonorbornane-2-carboxylic acid (BCH). The action of BCH displays strict stereospecificity and provides compelling evidence that the "phosphate flush" is independent of the transcellular entry of oxidizable fuels. The "phosphate flush" is initiated immediately prior to the onset of the "first phase" of stimulated insulin secretion and lasts one or two minutes longer. However, it persists in phosphate-free media, Ca++ free media, or when insulin release is inhibited by adding Ni++ to the perifusates. Thus, the heightened efflux of orthophosphate-^{32}P can be dissociated from insulin extrusion and from the net influx of ionic phosphate or calcium.

In view of its rapid onset and brief duration, we have attempted to evaluate whether the "phosphate flush" is linked to some immediate and transitory alteration in islet permeability incident to the union of stimulus with receptor site. Towards this objective, we have tested the effects of agents which stabilize membranes. Obtundation of "phosphate flush" and insulin release has been achieved with lipophibic local

anesthetics which are known to dampen membrane lability to ion fluxes
(i.e. 1.0 mM tetracaine), as well as with D_2O, an agent known to sta-
bilize the structural organization of many lipoproteins by inhibiting
hydrogen bonding. We have also tested glucose anomers to further assess
whether the "phosphate flush" is linked to early aspects of stimulus
recognition. Others have reported that the a-anomer of glucose selec-
tively protects islets against alloxan toxicity - a phenomenon that it
thought to occur at the plasma membrane of the islet beta cells - whereas
other aspects of glucose disposition by islets, such as transcellular
transport and intracellular phosphorylation do not display similar
anomeric specificity. We have now shown that the "phosphate flush"
occurs selectively in response to the a rather than the b anomer of
glucose. This anomeric specificity, when combined with the other data
cited above, is consistent with the proposition that the rapid transient
efflux of phosphate ions from pancreatic islets, in response to secretory
stimulation, may constitute a convenient biochemical probe for the
earliest events in islet excitation.

B. Summary

The underlying determinants of the "phosphate flush" remain to be
elucidated and it is likely that further research will provide even
better probes for monitoring early perturbations of the membrane stimulus
recognition site. However, pro tem, we have already used the "phosphate
flush" to establish that the faulty release of insulin from fetal islets
is due to later defects in the sequence by which stimulus and secretion
are coupled in islet tissue. More importantly, perhaps, our experience
with the "phosphate flush" has established the feasibility of trying to
find biochemical probes for temporal dissection of sequenced events in
complex cellular "work".

C. Recommendations

Efforts should be expanded towards developing additional probes for
monitoring discrete components (especially those having to do with
stimulus recognition) in "stimulus-secretion coupling." These will pro-
vide tools for assessing relative cell integrities following islet
isolation, culture and/or transplantation. They will also enable in-
trinsic islet anomalies as well as environmentally - or pharmacologically-
induced alterations in islet function to be classified on a pathophysio-
logical basis. The spin-offs need not be confined to islets and diabetes.
The similarities in the biochemical pattern of response during the tran-
sition from "rest" to many kinds of cellular "work" (see above) would
suggest that important new insights may be gained relevant to all situa-
tions in cell biology where excitation entails biochemical-bio-mechanical
transformations.

Fruitful growth will necessitate interdisciplinary approaches and the

prerequisite areas are ones in which there are limited numbers of adequately trained workers (e.g. cell isolation; tissue culture; membrane biochemistry; bioelectrical phenomena; ultrastructure; ion fluxes etc.). Greater fiscal support for ongoing studies and more training of future workers are the obvious recommendations. However, I believe that the former should receive the highest priority in the expectation that it will generate the latter. I particularly would favor support for small interdisciplinary clusters of 3-5 workers (although other types of funding should not be slighted). I believe that fruitful interdisciplinary interactions are most apt to evolve from such small groups where continuing physical and intellectual contiguity assures symbiosis. Provisions for the training of pre- and postdoctoral Trainees should be incorporated directly into the individual research awards by which they are funded. Training within such small working groups should yield broadly based cell biologists attuned to the multidisciplinary orientation that problem-solving in islet metabolism demands.

INSULIN AND GLUCAGON SECRETION IN MONOLAYER CULTURES

Wilfred Y. Fujimoto, M.D.

BACKGROUND AND PRESENT STATUS

True monolayers of mammalian pancreas or islet were first established in 1967. Since then, there have been a relatively few groups who have published results using this technique (Table). These include the following noteworthy developments:

1) Enrichment for endocrine cells and an inital removal of fibroblastoid cells by the decantation technique of Lambert and colleagues;

2) Monolayer cultures of cells dispersed from isolated islets by enzymatic digestion or by nonenzymatic mechanical dissociation;

3) Retardation of fibroblast growth through modification of the culture medium;

4) Demonstration that beta cells in monolayer cultures undergo cell division;

5) Establishment of monolayer cultures on artificial capillaries;

6) Recent reports of the maintenance of fetal human islets and rat islets in suspension culture or in soft agar for up to three months (the implication being that there are potential islet banks through such techniques).

It has been demonstrated by several laboratories that monolayer cultures of the endocrine pancreas secrete insulin and glucagon appropriately. (Several studies from the University of Washington were discussed which demonstrated these aspects, including investigations with somatostatin and ionophore A23187, as well as cultures in which selection for endocrine cells and against fibroblastoid cells was successful.)

The advantages of these monolayer cultures are:

1) The a and B cells may be examined independent of neurohumoral influences.

2) Each cell is fully exposed and equally exposed as other cells in the monolayer to the incubation medium.

3) These are living cells, not slowly dying cells as in other in vitro preparations. Because of this, repeated studies may be done on the same specimens, if necessary.

4) Relatively large numbers of specimens may be studied concurrently, and since cells are dispersed from a single cell suspension pool, these specimens are essentially identical.

5) Because the cells are in a monolayer, they are ideally suited for both routine and special morphologic studies.

Because of these attributes, there are certain kinds of investigation which are best performed by using these cultures rather than other in vitro methods. At the present time, however, there are also certain limitations to this approach:

1) This is a tissue culture method and therefore requires special experience and equipment.

2) Studies of hormone secretion are essentially static.

3) The cell population is mixed.

FUTURE PERSPECTIVES

The following are extremely important future areas of endeavor:

1) The establishment of monolayer cultures from human islets;

2) Further progress in selecting against fibroblastoid cells;

3) Methods for developing homogeneous a and B cell cultures through chemical selection (including immunologic selection) and cloning procedures (development of such homogeneous cell preparations must be considered one of the major potential benefits to be derived from these investigations and will in turn lead to the following studies);

4) The clarification of hormone synthesis and secretion in homogeneous   or B cell cultures, independent of a-B cell interactions;

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5)   The investigation of molecular processes involved in hormone synthesis and secretion;

6)   The investigation of a and B cell growth regulation;

7)   Cell hybridization experiments and investigation of cellular and molecular genetics;

8)   The growth of B Cells on culture supports that are suitable for implantation into diabetic recipients;

9)   The transplantation of B cells obtained from honogeneous B cell cultures;

10)   The development of methods for bulk culture of B cells (especially human B cells) for transplantation and for mass insulin production.

RECOMMENDATIONS

Through various in vitro techniques, much has been learned about insulin and glucagon secretion that probably would not have been possible through in vivo studies. In spite of these advances, however, many of the basic processes involved in the synthesis and secretion of these hormones remain unknown because of the unavailability of homogeneous a or B cell preparations. At the present time, the most promising source for such homogeneous cell preparations appears to be through monolayer cultures of the endocrine pancreas. Successful achievement of this objective will have rar-reaching implications in all spheres of research concerning insulin and glucagon synthesis and secretion as well as potential therapeutic applications. Thus, although the number of groups publishing in this area has increased about 5-fold since 1970, the actual number of investigators is still small and a further immediate increase of 3- to 5-fold would appear to be a conservative estimate in light of the above considerations. This increase will create an immediate need for cell biologists with tissue culture training who will be involved primarily in seeking optimal conditions for development of homogeneous a and B cell cultures. This need may be partly filled by recruitment of such individuals from other research areas. In addition, consideration should be given to the training of researchers who are already involved in diabetes investigation, in tissue culture techniques so that on-going studies using monolayer cultures of the endocrine pancreas may be continued to confirm and expand observations of insulin and glucagon synthesis and secretion made through other in vitro systems, and to ultimately extend these to homogeneous a and B cell cultures. Certain other disciplines will become intimately involved in this area as efforts are directed toward each of the future goals outlined in the previous section; these will include ultrastructural morphologists, immunologists, bioengineers, biochemists, molecular biologists, and cell geneticists.

The major portion of the research in this area may be performed by individual investigators. Centers, with their core laboratories and multi-disciplinary orientation, will be helpful in certain investigations such as the development of immunologic selection methods. Program projects, with their multi-faceted approach, are especially suited to investigations such as those concerning a or B cell biology and biochemistry as related to glucagon or insulin production. In the future, contract research may be feasible for determining methods for bulk culture of certain cell types.

SUMMARY OF REPORT ON SECOND MESSENGERS

Nelson Goldberg, Ph.D.

Investigations aimed at elucidating the biological importance of cyclic GMP in relation to cyclic AMP were summarized and the basis for developing the hypothesis that cyclic GMP and cyclic AMP promote opposing regulatory influences in a number of biological systems was explained. Support for this hypothesis was shown to derive from experiments demonstrating that exogenous cyclic GMP or cyclic AMP addition can mimic the effects of hormones that promote opposing regulatory influences and that the steady state levels of cyclic GMP are increased by agents such as polypeptide and neuro-hormones (including insulin), mitogens and steroids or conditions that promote cellular events opposite to those that increase cellular cyclic AMP concentration. The concept that cyclic nucleotides participate in the biological regulatory process in some instances without any change in their tissue concentration but as a result of a change in the profile of available cations (i.e., Mg^{2+} of Ca^{2+}) in the cellular milieu was also introduced and supported by the demonstration that the interaction of cyclic AMP or cyclic GMP with specific cellular proteins can be selectively altered or shown to be dependent upon calcium or magnesium.

It was also pointed out that new analytical procedures have been developed which allow for a more reliable measurement of cyclic GMP in biological material at a much greater level of sensitivity (i.e., 100 fold greater) than was ever available before. This and other advances in the cyclic nucleotide field will make it possible to examine more reliably and intelligently the role or roles played by both cyclic GMP and cyclic AMP in biological regulation.

The probability is very high that significant advances will be made in this area that will have a direct bearing on the mechanism by which the insulin molecule influences cellular function. The potential benefits of such basic information are very great. From the standpoint of diabetes, the information we in this field hope to obtain could conceivably provide a means for bypassing either defective insulin production, secretion or action by intervening at the level of the sensitive target tissue with a synthetic "messenger molecule" that would be designed to interact with identifiable cellular components involved in turning "on" or turning "off" metabolic steps that normally undergo such modifications if the insulin signal were properly generated and received.

INSULIN SECRETION AND ACTION

R. L. Jungas, Ph.D.

PART I: RESUME OF RESEARCH ON ACTION
OF INSULIN ON ENZYMES

During the relatively short period since 1970, reports have appeared from various laboratories documenting effects of insulin on the activity of the following six enzymes: (1) adenylate cyclase; (2) membrane ATPase; (3) phosphodiesterase; (4) pyruvate dehydrogenase phosphatase; (5) glycogen synthetase phosphatase and (6) glycogen synthetase kinase. In nearly every case these reports have been surrounded by controversy, occasioned by the difficulty of reproducing the effects in other laboratories; and in no case can the action of insulin on the enzyme be considered in any way understood. The list includes enzymes considered to be localized in the plasma membrane, in the microsome fraction, in mitochondria or soluble in the cytoplasm. Other speakers in this workshop have discussed in part the effects of insulin on the phosphodiesterase and the glycogen synthetase kinase. I would like to summarize some findings of our group on the action of insulin on pyruvate dehydrogenase phosphatase, the only enzyme of the group which is found in mitochondria. Particular interest focuses on the pyruvate dehydrogenase activation by insulin because its mito-chondrial location virtually insures its separation from the plasma membrane, commonly considered to be the primary site of action of insulin. Therefore, some type of cytoplasmic messenger or signal would seem to be required to transmit the effects of insulin from the primary site of action on the plasma membrane to the locus inside the mitochondria where the enzyme activity is altered. Identification of this cytoplasmic signal remains a major goal of investigations at this aspect of insulin's action.

To display the action of insulin on pyruvate dehydrogenase, it is necessary to expose intact fat cells to insulin. The tissue or cells may then be broken up, the activity of pyruvate dehydrogenase assayed in the extracts. When this is done, it is found that extracts pre-pared from insulin treated tissue contained approximately twice the pyruvate dehydrogenase activity of the controlled tissue. This is true, however, only if the tissue is incubated in the presence of bicarbonate during the exposure to insulin. The requirement for bicarbonate is not understood. A second requirement for the display of this action of insulin is that an oxidizable substrate be present in the incubation medium during exposure to insulin. This requirement can be satisfied

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by a sugar such as glucose or fructose, by pyruvate, or by intra-cellular glycogen in the special case of tissue used from fasted refed animals. This requirement for an oxidizable substrate is also not understood. A third matter requiring clarification relates to whether the cytoplasmic signal generated by insulin is conveyed by a unique second messenger or by a common intracellular metabolite such as a phosphorylated compound or fatty acid derivative. In our laboratory we have been unable to dissociate the action of insulin to activate pyruvate dehydrogenase from its action in diminishing lipolysis in adipose tissue. The possibility that the action of insulin on pyruvate dehydrogenase is mediated by a diminution of cyto-plasmic fatty acid or fatty acyl CoA is therefore an attractive one.

There are currently four groups focusing a major effect in clarifying the action of insulin on pyruvate dehydrogenase. Accordingly, there are four major theories concerning this action of insulin. The group headed by Professor Otto Wieland in Munich has proposed that insulin acts as follows: insulin by diminishing lipolysis and encouraging esterification of fatty acids would decrease the tissue level of fatty acyl CoA. Since fatty acyl CoA is an inhibitor of the adenine nucleotide translocator of the mitochondrial membrane, lowering the fatty acyl CoA level would promote the exit of ATP from and the entrance of ADP into the mitochondrial matrix compartment, thus lowering mitochondrial ATP/ADP ratio. This would reduce the activity of pyruvate dehydrogenase kinase leading to decreased phosphorylation and hence activation of pyruvate dehydrogenase. The theory is plausible but has no rigorous experimental support. It may well play a role in the overall effect of insulin on pyruvate dehydrogenase activity, but I think it unlikely to be the sole or even major means by which insulin influences this enzyme.

A second theory, that of Dr. Halperin in Toronto, also begins on the solid ground of assuming that insulin lowers the level of fatty acyl CoA in the fat cells. Halperin and his colleagues have described a citrate translocator in the mitochondrial membrane, which is inhibited by fatty acyl CoA. Thus by lowering fatty acyl CoA levels insulin would promote the exit of citrate from the mitochondrion. Mito-chondrial citrate impairs the activity of pyruvate dehydrogenase phosphatase either as a direct inhibitor of this enzyme or by chelating the calcium needed by the enzyme. Consequently a diminution in citrate would favor dephosphorylation of pyruvate dehydrogenase thus increasing its activity. This theory of Halperin is a very attractive one, and there is some indirect evidence that insulin may indeed lower the levels of mitochondrial citrate in adipose tissue. The theory does not, however, explain the action of insulin on pyruvate dehydrogenase phosphatase to be described shortly.

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A third theory has been generated by Drs. Denton and Randle in Bristol. They suggest that insulin increases the mitochondrial content of calcium, a cation required by pyruvate dehydrogenase phosphatase. Such an action could also account for the activation of pyruvate dehydrogenase. The theory has its attraction; there have been reports of an action of insulin to promote calcium entry into mitochondria, but the direct experiments to display mitochondria with both increased pyruvate dehydrogenase activity and an increased content of calcium have been negative. The theory is therefore at present without strong experimental backing.

The fourth theory, which I support, holds that insulin in an unknown manner causes an activation of pyruvate dehydrogenase phosphatase. Evidence for such an activation was presented at this meeting and has been recently published. The activation of the phosphatase must occur by a process which is only slowly reversible and could not be readily explained as secondary to changes in mitochondrial citrate or calcium concentrations, unless these changes in turn lead to enzymatic changes which impinge upon the phosphatase. It is very important that these phosphatase measurements be improved and that the insulin effect be confirmed in other laboratories.

If the finding that insulin activates pyruvate dehydrogenase phosphatase can be confirmed, it will be of great interest to consider whether other actions of insulin might also be mediated by increased protein phosphatase activities. I find such a concept quite attractive. There are reasons to think that the action of insulin on glucose transport and glycogen synthetase and on the hormone sensitive lipase may also at least in part result from an increased protein phosphatase activity. It is possible that insulin generates a unique second messenger which modifies protein phosphatase activity. Experiments designed to evaluate this hypothesis are urgently needed.

PART II: SIGNIFICANCE OF STUDIES ON INSULIN ACTION

Our understanding of the biochemical abnormalities underlying the diabetic condition will remain superficial and without focus so long as we lack a real understanding of the biochemical mechanism of action of insulin. Thus, our basic understanding of diabetes is crucially dependent upon research in this area. The impact of a major advance in our understanding of the action of insulin would go far beyond these theoretical considerations however. Intimate knowledge of the mechanisms by which insulin achieves its tasks in the body, should allow the chemist to devise alternative means of achieving these same tasks in

individuals lacking insulin. For example, if the action of insulin is mediated by a unique messenger, identification of this messenger and its synthesis by the chemist would provide us a material which could well duplicate many of the actions of insulin when administered to the diabetic. While the technical details involved in such thinking are at the moment highly conjectural, there can be little doubt that a great practical benefit would ensue to all diabetics from an important breakthrough in our knowledge of the mechanism of action of insulin.

Currently, something over 20% of the funds designated for diabetes research through the NIH are devoted to advancing our understanding of the mechanism of action of insulin. It would be a mistake to lessen our emphasis in this area of diabetes research. I would like to see about 25% of the funds devoted to studies on the mechanism of action of insulin.

SUMMARY OF REMARKS

Joseph Larner, M.D., Ph.D.

Our work has centered on the mechanism of insulin action to stimulate glycogen synthesis which is a universal action of insulin in all cells (so far as we now know). Two enzyme changes have been observed, the activation of the glycogen synthesizing enzyme by conversion from its inactive phosphorylated form to its active dephosphorylated form. The chemistry of this enzyme in terms of its control by phosphorylation is under study. The second is the inactivation of the protein kinase which is also under active study. This appears to be related to the reassociation of the enzyme from its two subunit parts. The third component of the system which we have identified and are studying is an inhibitor of the kinase which is rapidly formed in the presence of insulin and which may be a new second messenger. This is also under active study.

The control of the overall system by a novel diabetes producing peptide which is obtained from human pituitaries and from human diabetic urine is also under active study. Also, the influence of other peptides derived from growth hormone on this system are under active investigation. To determine the sensitivity of human diabetic tissues to insulin, cultured fibroblasts from controls and diabetic subjects are compared in terms of the sensitivity of these enzyme interconversions to the influence of insulin.

I feel that increased funding for diabetes research is now warranted because we can now ask the following question for the first time, "If the blood glucose for a diabetic subject could be controlled as precisely as that of a normal patient by an insulin delivery system yet to be developed which is precise enough to do the job, would the vascular complications of the disease be prevented?"

INSULIN RECEPTORS

Dean H. Lockwood, M.D.

In recent years it has become increasingly apparent that certain clinical disorders and metabolic states are associated with the phenomenon of insulin resistance. Generally, insulin-resistant states are characterized by an increase in basal levels of circulating insulin, excessive plasma insulin responses to numerous secretory stimuli and reduced effectiveness of endogenous and exogenous insulin both in vivo and in vitro. In the past several years advances in the field of hormone action have been sufficient to warrant investigations of the cellular alterations responsible for altered insulin sensitivity in pathologic states. Although the more recent studies have not been directly related to diabetes mellitus, I feel strongly that these studies and future studies of insulin resistance will have a significant impact on the understanding and ultimately the management of diabetes.

There are two main reasons why studies of insulin action and insulin resistance are relevant to diabetes.

1. Although it is clear that abnormal insulin secretion is a major problem in diabetes mellitus, there is increasing evidence that impaired insulin action may also be present. Thus a greater understanding of insulin resistance may prove directly relevant to the pathophysiology of diabetes mellitus.

2. Since obesity, caloric deprivation and caloric distribution can markedly influence carbohydrate tolerance in a diabetic, knowledge concerning the cause of these states of altered insulin sensitivity should also be of benefit to the diabetic.

Current knowledge concerning the mechanism of action of insulin suggests the following sequence of events occurs between insulin and the hormonally-responsive fat cell.

1. Insulin interaction with specific glycoprotein "receptors" on the surface of the cell membrane (primary reaction).

2. Transmission of information from insulin-insulin "receptor" complex to structures or processes regulating membrane and/or intracellular processes.

3. Modulation of processes which produce the terminal effects of insulin (stimulated transport, antilipolysis, glycogen, lipid and protein synthesis).

One aspect of our work has been an attempt to localize which of the above events is altered in obesity and thus, presumably, responsible for insulin resistance. Our laboratory and others have used adipose tissue from young (130-160 g) and adult (400-500 g) rats as a model system to investigate possible alterations that may contribute to insulin resistance. Fat cells from older rats (mean diameter ~75 µm) are larger and appear less sensitive to insulin stimulation of glucose oxidation than small cells (mean diameter ~45 µm) from younger animals. Different cell sizes rather than the age of the animals are reportedly responsible for the differences in responsiveness to insulin.

The possibility that insulin-cell association is involved in insulin insensitivity was examined by studies utilizing the insulin-like action of spermine and by determining the extent of [125I] insulin binding in large and small rat adipocytes. Spermine mimics the action of insulin on fat cells by acting at membrane sites separate from insulin receptors but which share a common pathway with insulin mediated responses. By virtue of its site of action, spermine would be expected to stimulate greater glucose oxidation in large cells than insulin if insulin resistance resulted from defective insulin-receptor interaction. However, the maximal spermine response of large cells was similar to the insulin response and both were one-half that of small cells. Studies of insulin binding showed that with saturating concentrations of [125I] insulin, the total insulin-binding capacities of large and small cells were equal. Furthermore, the affinity between insulin and insulin-binding sites was not diminished in large insulin-insensitive cells since specific binding of [125I] insulin at concentrations below saturation was similar in both groups of cells. These observations indicated that the alteration in large cells exists in a step subsequent to insulin binding.

In a further attempt to localize the defect, measurements of basal and insulin-stimulated uptake of D-glucose, 2-deoxy-D-glucose and 3-0-methyl-D-glucose were determined in small and large adipocytes. At the higher D-glucose concentrations employed, there were no significant differences between large and small cells in rates of D-glucose uptake in the absence of insulin (basal rates). However, at the lower D-glucose concentrations of 0.33 mM and 1.0 mM, the basal rates for large cells were significantly greater than those found with small cells. The "V_{max}" was similar for both cell types, but small cells had an apparent "K_u" value (conc. of D-glucose which gives one-half V_{max} for D-glucose uptake) which was twice the value of 1.0 mM calculated for large cells. Incubation of the fat cells with insulin enhanced D-glucose uptake particularly at lower D-glucose concentrations. The rate of uptake following stimulation by insulin was not significantly different between the two cell types at any sugar concentration used. Thus, following insulin stimulation, the "V_{max}" and "K_u" (0.43 mM) are similar for both cell types. The D-glucose uptake system was further

investigated by the use of 2-deoxy-D-glucose in an attempt to reduce metabolite formation and loss from the cells during the incubation period. The results were qualitatively similar to those found in studies using D-glucose.

The rate of uptake of a third sugar, 3-0-methyl-D-glucose, was used to study the D-glucose transport systems of large and small cells. 3-0-methyl-D-glucose uptake is a measure of only the D-glucose transport system since it is transported like D-glucose but not metabolized. No differences were observed between large and small cells for 3-0-methyl-D-glucose uptake either in the presence or absence of insulin stimulation.

Results of this study indicate that transmission of "signal" from the insulin-insulin "receptor" complex to the D-glucose transport system as well as the glucose transport system itself are not the sites responsible for the markedly diminished production of glucose metabolites following insulin stimulation in large adipocytes. Instead they suggest that other intracellular processes are involved.

Studies of the insulin "receptor" have been extended to human obesity. Subcutaneous abdominal fat tissue was obtained from nine morbidly obese patients and eight normal weight subjects. The fat cell volume was roughly five times greater in obese subjects. Binding to large and small cells was similar over concentrations of [125I] insulin ranging from 1.2×10^{-10} to 5×10^{-9} M. When expressed as [125I] insulin bound per cell, there were again no differences between large and small cells. Under these experimental conditions there was no significant insulin or "receptor" degradation. The affinity of the insulin receptor for its hormone was examined by measuring the displacement of [125I] insulin by native insulin in adipocytes from obese and normal weight subjects. The concentrations of native insulin necessary to displace 50 percent of the maximum specific binding were 2.17×10^{-9} M for small adipocytes and 1.75×10^{-9} M for large adipocytes. These findings indicate that this parameter of adipocyte insulin-receptor interaction is also unaltered in obesity.

Adipose tissue is at least one tissue-site where the insulin resistance of obesity might be located. In contrast, some investigators have been unable to demonstrate insulin resistance in large human fat cells. Also, it is unlikely that adipose tissue accounts for the totality of the insulin resistance of obesity since only a small fraction of ingested glucose is metabolized by adipose tissue. Furthermore, both muscle and liver of obese subjects have been shown to be insulin resistant by forearm perfusion and splanchnic exchange studies respectively. Thus, the primary insulin resistance of obesity could be in liver and/or muscle and the possible role of a decrease in insulin receptors in these tissues should be examined. It is possible the

finding of decreased specific insulin binding to circulating "monocytes" from obese patients is a reflection of the insulin receptor status in muscle and/or liver.

The site of apparent insulin resistance of large human adipocytes is unknown. Our data indicate that the initial step in insulin action, the interaction of insulin with specific receptors on the plasma membrane, is not involved. Whether there is a true insulin resistance in large human fat cells, i.e., an inability of insulin to stimulate glucose transport by direct measurement of this transport, has not been studied. Recently it has been shown that the activities of several enzymes are altered in large human adipocytes and, as postulated for large adipocytes from adult rats, alterations in intracellular metabolism may underlie the apparent insulin resistance of large human fat cells.

Additional work in our laboratory and others indicates that the cellular basis(es) for other insulin-resistant states is different than that for obesity. For example, in Cushing's syndrome, it appears that intracellular glucose metabolism (hexokinase), glucose transport and insulin binding are all altered.

As regards future significant research in the area of insulin action in normal and resistant states, it seems to me we have adequate manpower in some disciplines and a dearth in others. In consideration of the latter, membrane physiologists and chemists are needed as well as organic and physical chemists with an interest in hormone action. My recommendations for increasing significant productivity in our research area are as follows:

1. Increase funding for individual research grants. Many established investigators in the field would be more productive if their research operations were financially secure. At present, many investigators must supplement their NIH funds by applying for numerous small grants or by receiving significant support from their parent institution. Frequently, the non-research demands placed on a scientist receiving significant support from his institution are detrimental to his research efforts.

2. Medical scientist program for diabetes. Young physicians with an avowed interest in diabetes (or related) research would receive support for post-doctoral training in those areas in which manpower is lacking. In order for this program to be worthwhile, the manpower needs would have to be clearly established and the laboratories capable of developing these young scientists defined. The long-term results would probably

be greatest if the "developmental" laboratories were <u>not</u>
presently entrenched in endocrine research.

3. Recruitment of PhDs capable of fulfilling manpower needs.
   Once the manpower needs are established, members of The
   National Commission on Diabetes should establish communication
   with those graduate programs which are capable of training
   PhDs in the needed areas. Faculty, as well as young graduate
   students, should be informed about the "current state of the
   art" concerning hormone action, the projected manpower needs
   and the future opportunities available.

METABOLISM OF PANCREATIC a- AND B-CELLS

FRANZ M. MATSCHINSKY, M.D.

The a- and B-cells of the pancreas have the ability to quantitate the fuel supply of the organism and to maintain optimal blood levels of calorigenic molecules through the two major hormones glucagon and insulin. Even though these cells play such a prominent role in the regulation of intermediary metabolism, research has hardly been sufficient to explore the unique biochemical features of these cells. Of many aspects only the surface has been scratched. I list here 10 high priority areas for research in islet biochemistry and discuss three of these and certain methodological approaches in somewhat more detail.

Table 1

High Priority Areas of the Biochemistry of Islet Cells

1) Multiple actions of glucose on islet cells.
2) Interactions of glucose with other fuel molecules.
3) Possible linkage of glucose metabolism and insulin biosynthesis.
4) Possible linkage of intermediary metabolism and glucagon biosynthesis.
5) Energy metabolism
6) Phosphate metabolism
7) The role of Ca^{++}
8) The role of cyclic nucleotides
9) The role of prostaglandins
10) The role of phospholipids

As to methodology two eminent problems are pointed out: 1) the need for procedures to obtain relatively pure a- and B-cell preparations and 2) the need for detailed morphologically and biochemically well controlled studies on subcellular fractionation of islet tissue. Even though projected advances of tissue culture may provide pure a- and B-cell cultures, it would seem wise to continue using the classical procedures of quantitative histochemistry, allowing the isolation and biochemical study of relatively pure a- and B-cell samples in a number of well defined in vivo and in vitro systems currently employed for islet research. Even with the most spectacular success of tissue culture methods we would need to know how a- and B-cells function in a normal setting. Subcellular fractionation of islets has been shown to be feasible. The methods should be perfected and should become more widely used. ATPases, adenylate - and guanylate cyclase and prostaglandin synthetase need to be studied in such systems and the possibility of studying binding of islet cell specific ligands (i.e. alloxan) needs to be explored. Studies on the membrane receptors for various high affinity modulators of islet cell function would seem feasible.

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Of the topics listed as high priority areas of research in islet cell biochemistry three stand out in my view.

Firstly, the multiple actions of glucose on islet cell both metabolic and functional. There remains the fundamental puzzle how increasing glucose levels lead to the well documented dramatic increase of glucose usage paralleled by throttling the consumption of other fuels. Studies need to be continued on the regulation of islet cell intermediary metabolism. These studies need to be systematic and wide ranging. Much of the published literature on that score is piecemeal.

Secondly, the role of cyclic nucleotides in a- and B-cell function needs to be further explored with vigor. The glucose induced rise of cyclic-3'5'-AMP and of insulin release are both Ca^{++}-dependent. The interplay between Ca^{++} conductivity and adenylate cyclase needs to be examined in great depth. Countless experimental designs and tools come to mind to pursue this line of research. Of particular importance would seem those involving phosphorylation and dephosphorylation reactions through protein kinases and phosphoprotein phosphatases.

Thirdly, there has been a revival of interest in the mode of alloxan toxicity in B-cells. Alloxan specifically interacts with metabolizable and non-metabolizable hexoses on the B-cells against the poison. The physicochemical properties of the site protecting against alloxan are very similar to those of the site involved in hexose mediated insulin release. Even though alloxan is a highly labile substance there is the possibility that this substance might bind covalently to specific sites on the B-cells and that this binding might be useful as a membrane probe specific for the B-cells, i.e. might be an extraordinary tag of the postulated glucoreceptors. Again numerous experiments come to mind to make use of these provocative findings.

I believe that solving problems like those just described will bring us closer to understanding of normal and pathological (i.e. diabetic) islet cell function. Even if we don't find an immediate cure for diabetes through this research it will make the active researchers better teachers of medical students and students better doctors leading to more appropriate care for the large number of diabetics.

METABOLISM OF PANCREATIC ISLET CELLS

Franz M. Matschinsky, M.D.

The a- and B-cells of the pancreatic islets play a crucial role in regulating the bodies fuel supply. These cells are capable of measuring the minute to minute changes of the blood levels of the building units of the major three food stuffs (carbohydrate, protein and fat) and to respond to such changes with an appropriate output of glucagon and insulin. Table 1 lists the most important known small calorgenic molecules which function as stimulators or inhibitors of islet cells or have proven to be inert. It is essential to realize in this connection that many other physiological

Table 1

THE a- AND B-CELLS AS FUEL RECEPTORS

Stimulators	Inhibitors	Inert Molecules
	a-Cells	
amino acids	glucose	lactate
amino acid deriv.	mannose	pyruvate
acetoacetate	glyceraldehyde	glycerol
fatty acids	polyols?	
	B-Cells	
glucose	mannoheptulose	lactate
mannose	2-desoxyglucose	pyruvate
fructose		glycerol
glyceraldehyde		
polyols		
amino acids		
amino acid deriv.		
fatty acids		
ketone bodies		

modulators of fuel induced hormone secretion from a- and B-cells exist: e.g. neurotransmitters, peptide hormones, and ions. A priori there are at least three mechanisms through which pancreatic islet cells could recognize and quantitate fuel molecules:(1) directly via specific receptors located at the cell membrane (as proposed by the Receptor - or Regulator Sites Hypothesis)(2) indirectly through alterations of metabolite and cofactor levels of intermediary metabolism (as proposed by the Metabolism or Substrate Site Hypothesis) and (3) through mechanisms which

INSULIN RELEASED, μU/I00 islets x ml
GLUCOSE USED OR LACTATE FORMED,
pico moles/islet x hr
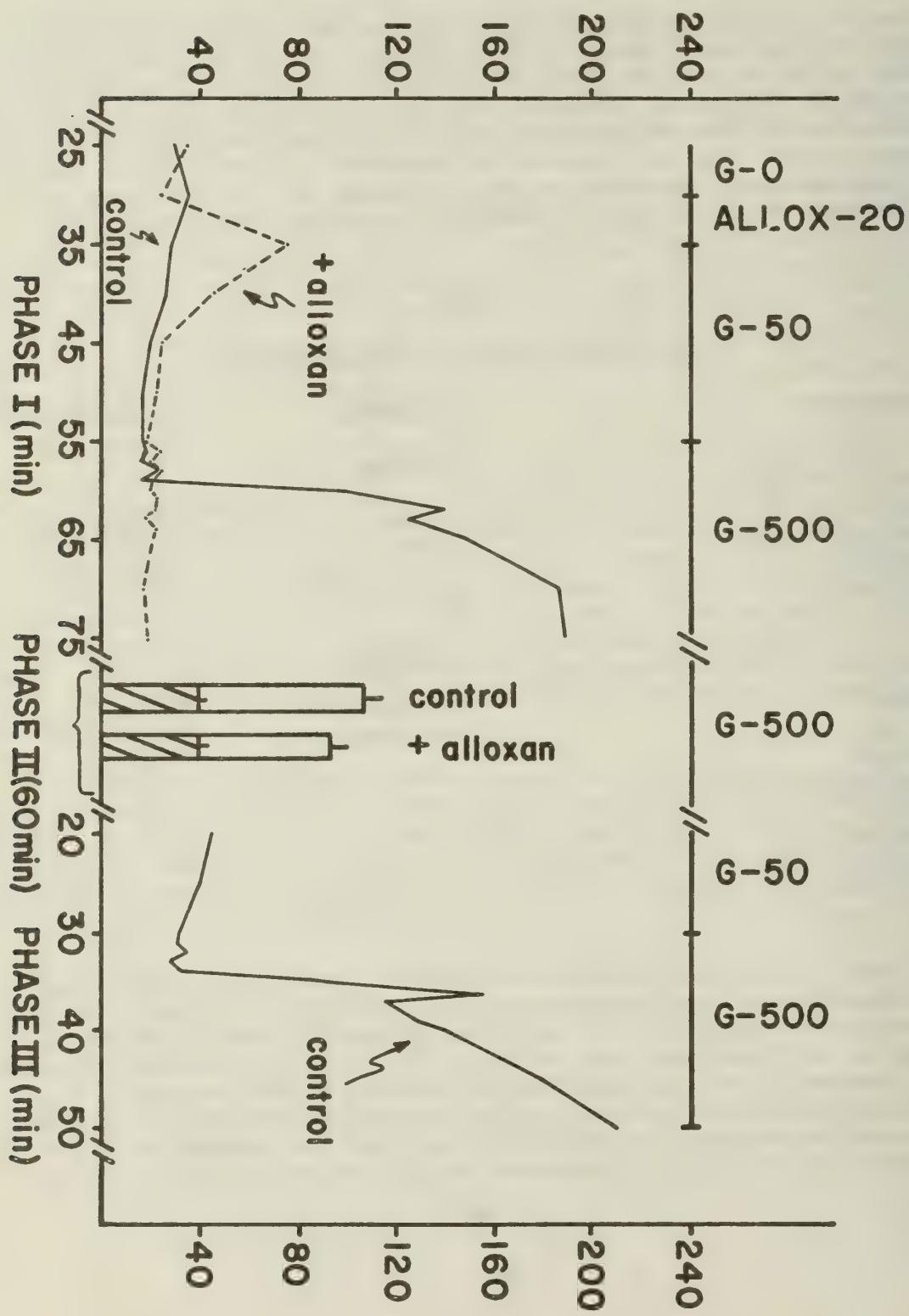
involve both membrane receptors as well as metabolic processes (as proposed by the Dual Function Hypothesis).

From this it is obvious that the elucidation of the intermediary metabolism of pancreatic islet cells is an eminent aspect of islet cell research. Fortunately, there are suitable biological procedures for studying the metabolism of pancreatic islets. In vivo studies can provide some insight and are the major approach for studies in man. For in vitro studies the isolated perfused pancreas, isolated perifused or batch incubated islets, tissue cultures and suspensions of islet cells are now highly feasible systems. One of the difficulties arises however from the lack of methods allowing the simultaneous recording of metabolic fluxes and hormone release. One possible solution to this problem might be the alternate study of isolated islets in the perifusion chamber for kinetics of hormone release and in a small incubation vial for measuring parameters of fuel handling (Figure 1). In Phase I and III insulin release is measured in the perifusion system and during Phase II the islets still attached to a millipore filter are incubated in a glass vessel to measure glucose usage and lactate formation. Another difficulty, only partly resolved, lies in the cellular heterogeneity of the pancreatic islets. Such studies with relatively pure a- and B-cell populations have nevertheless been performed. Also available are powerful tools for quantitating the uniquely small amounts of metabolites and cofactors of metabolism or for recording rapid metabolic changes within islet cells (Table 2). Some of these analytical procedures have not

Table 2

ANALYTICAL PROCEDURES FOR STUDYING METABOLISM
OF PANCREATIC ISLET CELLS

1) Enzymatic fluorometric procedure
2) Radiometry
3) GLC
4) GLC- Mass spectrometry
5) Immunochemical procedures
6) Receptor assays
7) Surface fluorometry or spectrophotometry
   combined with electrophysiology (for
   studying rapid kinetics)

been applied yet to islet research (i.e. # 6 and 7). But there is no reason why they couldn't be.

One of the central issues of islet cell intermediary metabolism is the nature of glucose handling, since glucose affects almost all aspects of the metabolism and function of these cells. At least 9 different actions of the

glucose molecule can be listed (Table 3). Not a single one of these

Table 3

MULTIPLE ACTIONS OF GLUCOSE ON ISLET CELLS

1) Stimulation of insulin release
2) Permissive action allowing other molecules to
     cause IRI release
3) Induction of electrical activity in B-cells
4) Inhibition of glucagon release
5) Stimulation of metabolism (CO_2 and lactate formation)
6) Increase of Ca^{++} uptake
7) Induction of phosphate and myoinositol release
8) Induction of cAMP rise
9) Stimulation of insulin biosynthesis

multiple actions is yet understood on a molecular level. There are good
reasons for postulating that metabolic signals arising in the course of
glucose metabolism are the basis for the many functions of glucose (Table
4). However, there are also numerous findings suggesting the presence of

Table 4

FINDINGS IN SUPPORT OF METABOLISM HYPOTHESIS

1) Order of potencies of hexoses to release insulin and to serve
    as substrates for metabolism is claimed to be the same.
2) Dose dependency of glucose usage, CO_2 and lactate production,
    insulin release, Ca^{++} uptake, activation of adenyl cyclase
    system, induction of electrical activity are all, within
    experimental error, superimposable.
3) Mannoheptulose and 2-desoxyglucose (hexokinase blockers) inhibit
    glucose induced release and all responses listed under # 2.
4) Certain substrates feeding into the glycolytic pathway are power-
    ful IRI releasers (i.e. glyceraldehyde).
5) Glucose is the most suitable substrate for maintaining ATP in
    islets.
6) In mouse islets there are rapid and concentration related changes
    of glucose metabolites related to IRI release.

glucoreceptors in islet cells (Table 5). The controversy can probably be
resolved within the near future through intensive research. Some of the

Table 5

FINDINGS SUGGESTING THE PRESENCE OF GLUCORECEPTORS IN ISLET CELLS

1) Sugars which are not slowly metabolized or not metabolized at all stimulate IRI release or potentiate release due to other stimulants.
2) Sugar alcohols, which usually penetrate cells only very slowly, cause abrupt insulin release.
3) The a-anomer of glucose is a more powerful stimulant of insulin release and inhibitor of glucagon release than the B-anomer.
4) Iodoacetate dissociates releasing and fuel function of glucose on a- and B-cells.
5) Metabolite and cofactor profiles change little or not at all in the rat islets exposed to high glucose.
6) The B-anomer of glucose is metabolized more rapidly and leads to a more pronounced accumulation of glucose-6-P than the a-anomer.
7) Alloxan blocks the glucose induced IRI release and cAMP rise but has only marginal effect on these parameters when glyceraldehyde is the stimulus.
8) Glucose penetration and ATP levels of a-cells are unrelated to glucose suppression of a-cells.

possible approaches are listed (Table 6).

Table 6

HOW CAN THE CONTROVERSY BE RESOLVED?

1) Further judicious exploration of the apparent coupling between hexose metabolism and insulin release or inhibition of glucagon release by studying the nature of hexokinase(s) of a and B-cells, by employing iodoacetate, iodoacetamide and alloxan, by performing detailed concentration dependency studies with hexoses, by comparing the actions of glyceraldehyde and dihydroxyacetone.
2) More detailed SAR studies under optimal in vitro conditions.
3) Further functional and metabolic studies of the anomeric specificity of glucose stimulation and inhibition of B- and a-cells, respectively.
4) Intracellular application of metabolites and cofactors of metabolism and recording of electrical responses.

Equally important aspects of islet cell function are the respective roles of Ca^{++} and cyclic nucleotides. There is no question that glucose causes increased Ca^{++} uptake by islet cells and induces an elevation of cAMP

levels. It is likely that both processes, the increased Ca^{++} conductivity of islet cell membranes and the activation of adenyl cyclase (which is the most plausible explanation of the cAMP rise), are obligatory events in the process leading to insulin release. To better understand the roles of Ca^{++} and cAMP it will be necessary to learn more about the biochemistry of the microtubular - microfilamentous systems and about the involvement of cyclic nucleotide dependent phosphorylation and dephosphorylation reactions through protein kinases and phosphoprotein phosphatases. In this connection it is ' worth pointing out that detailed studies of the phosphate metabolism of pancreatic islets have yet to be performed.

It is impossible to present an exhaustive discussion of all aspects of all aspects of islet cell metabolism. Certain high priority areas for research of the biochemistry of islet are merely listed in Table 7.

Table 7

HIGH PRIORITY AREAS OF THE BIOCHEMISTRY OF ISLET CELLS

1) Multiple actions of glucose on islet cells
2) Interactions of glucose with other fuel molecules
3) Possible linkage of glucose metabolism and insulin biosynthesis
4) Energy metabolism
5) Phosphate metabolism
6) The role of Ca^{++}
7) The role of cyclic nucleotides
8) The role of prostaglandins
9) The role of phospholipids

Many of these anticipated studies will almost certainly be performed in normal laboratory animals. It becomes however increasingly important to search for suitable animal models to study diabetic alterations of islet cell metabolism. Several such modesl have already been used successfully in initial studies (Table 8).

Table 8

ANIMAL MODELS FOR STUDYING THE PATHOPHYSIOLOGY OF PANCREATIC HORMONE RELEASE

1) Genetically obese hyperglycemic mice and rats
2) Chinese hamsters
3) VMH lesioned animals
4) Starvation diabetic animals
5) Alloxan and streptozotocin diabetic animals

Altogether we seem to be in a fortunate position enabling us to define clear objectives for research in islet cell metabolism and we have powerful biological and chemical analytical tools at hand for reaching these objectives. One of the the major difficulties seems to be in establishing effective teams and maintaining them over reasonably prolonged periods. Another problem is the danger of duplication of efforts. A certain degree of extended financial security for such teams and a sensible central planning seem to be mandatory for successful and economical solutions of the problem outlined.

SUMMARY OF REMARKS

Howard E. Morgan, M.D.

Studies of the metabolic effects of insulin have continued for the past twenty-five years. During the past five years there has been a substantial increase in research dealing with the effects of the hormone on protein turnover. These studies have involved investigation of the process in tissue culture, organ culture, perfused organs and intact animals and man. In the bulk of these studies, it has been possible to demonstrate that insulin both stimulates protein synthesis and inhibits protein degradation. Some earlier results that were in conflict with these conclusions were compromised by inappropriate control of the specific radioactivity of precursor pools.

Within this area of research, a number of topics require additional investigation. These include control of mRNA translation, description of the pathway of protein degradation and isolation, and description of the function of lysosomes. In approaching this problem, a multi-disciplinary attack would be particularly beneficial. This would need to combine some aspects of molecular biology, enzymology and electron-microscopy. These processes involve cellular organelles that are located on membranes and enclosed within membranes, necessitating some correlation with the metabolic and anatomical changes. This type of investigation has considerable importance in relation to the catabolic effects of insulin deficiency, and with the production of nitrogenous waste products in varying degrees of renal failure. In the next five years, I would estimate that a doubling of expenditures within this area would result in considerable headway. The investigators to utilize this level of support are at hand, and many of the techniques are now worked out. Training of additional investigators is also of importance. Approximately 20% of the funds within the area should be devoted to this purpose.

DISCUSSION OF INSULIN RECEPTORS AND
PHOSPHODIESTERASE ACTIVATION

C. R. Park, M.D.

The evidence is very strong that fat cells of the rat have a binding protein for insulin with a K_d of 3-6 nM. This binding protein is likely to be a "receptor," i.e., an element which generates a physiological signal mediating some insulin effect(s), but other functions, such as transport of insulin across the cell membrane, cannot be excluded. Until the signal is characterized, identification of the membrane binding protein as a receptor is uncertain. Only about two percent of the binding protein sites need to be in combination with insulin for a stimulation of glucose conversion to CO_2 and fat to be apparent.

Some recent studies by T. Kono at Vanderbilt (J. Biol. Chem., in press) on the activation by insulin of the low K_m, hormone bound phosphodiesterase of rat adipocytes by insulin are as follows: The insulin effect on the enzyme is rapid ($\sim$ 5 min) but requires exposure of intact cells to the hormone (1 nM). Activation is blocked by EDTA and several other metal chelators and also by sulfhydryl reducing or blocking agents. Chelator effects are not reversed by Mg, Mn and/or Ca. The enzyme is not in the plasma membrane but is probably in the endoplasmic reticulum. ^{125}I-insulin binds initially to the plasma membrane fraction, but, within five minutes in intact cells, substantial amounts of radioactivity are found in another membrane fraction. This fraction does not correspond exactly to that containing the phosphodiesterase.

These studies suggest that (1) insulin may enter the cell rapidly. It is possible that an intracellular site is necessary for some actions of the hormone; (2) activation of diesterase does not appear to involve a direct interaction between hormone and enzyme. Some "messenger" may be an intermediate; (3) activation probably involves chemical modification and this may be stabilized by heavy metal catalyzed oxidation.

It is important to understand the molecular basis of insulin action. This knowledge could possibly lead to methods for controlling the direction and intensity of insulin effects in clinical situations.

COMMENTS FOR NATIONAL COMMISSION ON DIABETES CONCERNING PATHOPHYSIOLOGY
AND NEUROENDOCRINE CONTROL OF THE PANCREATIC ISLETS

DANIEL PORTE, JR., M.D.

The Islets of Langerhans can be conceived of as a metabolic integrator in which the a and B cells respond to substrates, hormones and neural signals to provide for the secretion of insulin and glucagon in such a way that there is a coordinated flux of substrate between organs. The primary level of control is the circulating concentrations of the three substrates themselves - glucose, amino acids and free fatty acids. However, superimposed upon this direct regulatory system are hormonal signals and neural signals which modulate the effects of the direct substrate regulators. This modulation appears to provide information for long-term integration of islet cell function with body needs and to adjust islet function in relationship to the intermittency of the feeding pattern in mammals. The neurohumoral signals are of two types. Those that are primarily direct that have regulation of the final release process (release control) and those that are unable to effect alterations of hormonal secretion per se but change the sensitivity of the secretory mechanisms to other primary stimulators and inhibitors ("set point" control). The representatives of this latter class of "set Point" controllers are thyroxin, growth hormone, cortisol, estrogens and placental lactogen. Alterations in the steady state concentration of these hormones over time produces alterations in the responsiveness of the islet to other stimuli. The nature and the mechanism of this form of control is totally unknown but may involve the number of cell surface receptors, the coupling efficiency of receptors to the release process or to regulation of hormone synthesis.

Release control occurs by regulation of the later stages of the release process. Most peptide hormones and neurotransmitters, such as acetylcholine, epinephrine, norepinephrine, and serotonin are involved, as well as neurally related substances, such as the prostaglandins and somatostatin. Regulation can be either inhibitory, stimulatory, or both stimulatory and inhibitory. Acetylcholine is representative of a compound that is stimulatory for both insulin and glucagon and has no inhibitory properties. Somatostatin (now an islet hormone from the D cell) is representative of a type of hormone that inhibits both insulin and glucagon release and has no stimulatory effects. The indoleamines, catecholamines and prostaglandins appear to be mixed stimulators and inhibitors. In this case, net stimulation or inhibition depends upon receptor availability and the availability of other stimulators and inhibitors of insulin release. Since intra-islet glucagon can influence intra-islet insulin secretion and intra-islet serotonin and prostaglandins can influence intra-islet catecholamine, secretion and insulin release, the opportunity for complex interactions is readily available. The importance of the parasympathetic system during the feeding response and the sympathetic

system during a variety of stress states have been described in detail. However, the central controlling system and the afferent inputs for these responses have not been identified, nor have the mechanisms for the inhibitory processes elucidated.

Recommendations:

Studies should now be directed at the mechanism of action of stimulatory and inhibitory release controllers, the relative importance of the various controllers, the interaction between these systems, afferent inputs into these systems and the central systems responsible for integration. Such studies will require the disciplines of anatomy, biochemistry, physiology and psychology and clinical medicine to interact. Interdisciplinary studies will, therefore, be essential.

The training of investigators who have knowledge of at least two of these fields of study will be required as there are very few, if any, at the present time. Since the essence of research in this area is interdisciplinary approximately 20-30% of total dollars should be related to multidisciplinary support of some sort, i.e., diabetes program project or diabetes centers. The bulk should be related to individual investigator initiated programs. In contrast, contracts or development programs would not be suitable for this area except for the possible question of the development of somatostatin or its analogues as therapeutic agents.

Specialized facilities and techniques for studies in this area include:

1. Centralized analytical laboratories so that multiple hormones can be assayed in the same study.

2. Facilities for study of unanesthetized animals. Most primate centers provide such facilities, but they may need expansion.

3. Development of remote analytic techniques for blood sampling of unrestrained animals.

4. Development of methods to measure nerve traffic to islets and the analysis of electrical activity of single islet cells.

ASSESSMENT OF BETA CELL SECRETORY FUNCTION IN DIABETIC PATIENTS

ARTHUR H. RUBENSTEIN, M.D.

During maturation of the beta-cell secretion granule, proinsulin is converted into insulin and C-peptide, along with the release of several basic amino acids. In the pancreas there is one insulin molecule for each C-peptide molecule, and the two peptides are secreted into the portal vein in equimolar concentrations. Because of differences in their hepatic and peripheral catabolism, the molar concentrations of C-peptide are higher than those of insulin in peripheral blood. However, there is a sufficiently good correlation between the two so that C-peptide concentrations accurately reflect beta-cell secretory activity. This relationship has proved to be particularly useful in situations where measurement of insulin itself is not practical, such as in the patient with circulating insulin antibodies and/or the patient receiving exogenous insulin.

C-peptide is measured by a radio-immunoassay. Because it is a relatively poor antigen, it has been difficult to obtain large amounts of C-peptide anti-serum, and therefore the assay has not been widely available. However, the preparation of large amounts of synthetic human C-peptide has been recently carried out, and we therefore anticipate that measurement of C-peptide will be widely available in the near future. It is important that human C-peptide (either natural or synthetic) be used both to stimulate antibody production and as the standard in the assay. Because there are substantial differences in the amino acid sequences of C-peptides from different species, there is little cross-reactivity between various C-peptides in the assay. Thus, endogenous human C-peptide may readily be measured in the presence of bovine or porcine C-peptide or proinsulin. There is, however, a moderate degree of cross-reactivity with human proinsulin. For this reason, we generally refer to results as "C-peptide reactivity," or CPR. In normal subjects the concentration of proinsulin (on a weight basis) is only 1/10 that of C-peptide, and the C-peptide antiserum reacts 1/10 to 1/3 as well with proinsulin as with C-peptide. Therefore, in most patients proinsulin accounts for less than 3% of measured CPR. However, in insulin-treated diabetic patients, circulating insulin antibodies may bind substantial quantities of proinsulin which then is measured in the C-peptide assay and elevates the basal CPR level. However, the concentration of antibody-bound proinsulin tends to remain stable over short period of time, so that changes in CPR during, for instance, a glucose tolerance test still serve to measure beta cell secretory activity.

C-Peptide Measurement in the Diabetic Patient

Our understanding of the pathogenesis of diabetes mellitus has been advanced by measurement of serum insulin levels. However, the appearance of circulating insulin antibodies has hindered such studies in the insulin-requiring patient. By measuring C-peptide instead of insulin, we gained

a greater understanding of the state of beta-cell function in diabetes. For instance, both insulin and C-peptide levels are very low or unmeasurable during episodes of ketoacidosis. Following recovery from ketoacidosis, increases in serum CPR suggest that there is partial recovery of beta cell function. Thus, the occurrence of diabetic ketoacidosis in a patient does not necessarily imply that irreversible beta cell damage has occurred, but that functional impairment as well as cellular destruction of beta cells may be present. The remission phase of juvenile-onset diabetes, the so-called "honeymoon period" or "Brush effect," also appears to be due to partial recovery of beta cell secretory capacity. Comparative studies of stable and unstable diabetes have been facilitated by C-peptide measurements. Adult insulin-requiring patients who showed stable control, on the basis of diurnal plasma and urine glucose variability, had greater CPR levels than unstalbe patients, both in the basal state and following stimulation with either glucose or arginine. In the unstable group, basal CPR levels were at the lower limit of sensitivity of the assay, and showed no response to either glucose or arginine. It would thus appear that "brittle" diabetes is due, at least in part, to a more complete loss of beta cell secretory function.

Measurement of Free and Total Insulin in the Diabetic Patient

Methods have been developed to separately quantitate that insulin which is circulating in the "free" state and that which is bound to circulating anti-insulin antibodies in the serum of diabetic patients. The method involves precipitation of the high molecular weight serum proteins, including insulin antibodies, with polyethylene glycol (PEG) before and after sample acidification. Assay of the supernatants then gives values for free and total insulin. Combining this technique with that of the C-peptide assay, allows one to measure not only free and total insulin, but separately quantitate the contribution of endogenous and exogenous insulin to the prevailing serum level.

Measurement of Urinary C-Peptide and Insulin

Preliminary studies now indicate that it is possible to assess beta-cell function over a prolonged period of time by measurement of urinary C-peptide levels. The possibility of assaying C-peptide in the urine is attractive because measurement of serum insulin or C-peptide concentration reflects the combined effect of secretion and metabolism, while their measurement in the urine could potentially provide an integrated measure of beta cell secretory activity. Estimation of urinary C-peptide rather than insulin is advantageous because preliminary studies in normal subjects have shown that the urinary clearance of C-peptide is 7 to 12 ml/min. compared to the urinary clearance of insulin of only 0.2 to 0.7 ml/min. The immunoassay method for urinary C-peptide has been validated by showing that urine volumes up to 0.2 ml do not interfere with the assay, C-peptide added to urine can be quantitatively recovered, serial urine dilutions parallel the C-peptide standard curve, and urine C-peptide elutes in fractions corresponding to C-peptide standards on

gel filtration with BioGel P-30. We have found that normal subjects excrete 39 $\pm$ 4 µg C-peptide per 24 hours, which we estimate to be 3 to 5% of the C-peptide secreted by the beta cells daily. Young adults with juvenile-onset diabetes excrete 1.1 $\pm$ 0.5 µg C-peptide/24 hours, and adult onset diabetes average 24 $\pm$ 7 µg/24 hours, but with a wide range. Urine C-peptide measurement appears to be a useful parameter of beta cell function, especially in children in whom frequent blood determinations are difficult.

Conclusions

These new techniques have now provided the opportunity to study a number of important questions regarding beta cell function in diabetes. Ideally, funds should be made available to study these questions. Amongst the most important from my perspective are:

1. Make C-peptide widely available to investigators by the production of sufficient specific antiserum.

2. Confirm relationship of residula C-peptide secretion and diabetic control.

3. Investigate therapeutic approaches that may lead to pre-servation of residual beta cell secretion after the "honeymoon" period.

4. Study natural history of beta cell function in juvenile onset diabetes, particularly in relationship to time since onset of the disease, diet, therapy etc.

5. Determine relationship of residual beta cell function to long term complications.

6. Development of methods to measure beta cell secretory rates (from plasma and urine C-peptide measurements).

7. Application of C-peptide to monitor success of islet trans-plantation.

BETA CELL DYSFUNCTION IN DIABETES

ARTHUR H. RUBENSTEIN, M.D.

With the development of an immunoassay for insulin, it has become increasingly accepted that diabetes usually results from some degree of secretory failure of the pancreatic beta cells. In juvenile diabetics the extent of this failure is severe and is reflected in gross destruction of islet tissue. In adult diabetics, secretory failure is less pronounced, but when patients are carefully classified so that variables, such as obesity, are controlled, some degree of impairment of insulin secretion is almost always observed. In the glucose tolerance test there is both a quantitative decrease in total insulin secretion, as well as a sluggish early response with a tendency for the peak level to occur later than normal.

Whether the time course of the insulin response provides a significant clue to the nature of this defect is a controversial question, which has received much attention (Cerasi and Luft, 1973), especially in terms of the concept of two separate phases of insulin secretion, an early rapid burst followed by a later, more prolonged phase (Curry et al., 1968). On the other hand, the initial delay in secretion generally correlates well with the tendency in these tests for the blood sugar level to rise to higher levels and to peak at later times. It has been claimed on the basis of these results that islet cells of diabetics may have an inherent or acquired alteration in their sensitivity, or ability to respond to a glucose stimulus. This concept is also supported by the observations that other stimuli to insulin secretion, such as tolbutamide and glucagon, elicit normal secretory responses in mild diabetics, at a time when the response to glucose is already impaired (Simpson et al., 1968).

Studies of the pathologic changes in the pancreatic islets in adult onset diabetes support the concept of a primary failure of islet responsiveness. Gepts (1972) has pointed out that there is almost invariably a reduction in total islet tissue mass in the diabetic pancreas, amounting to approximately 50 percent in many cases. Moreover, there is a reduction of insulin stores in the surviving pancreatic beta cells of these individuals as evidenced by partial degranulation of the islet tissue and by a decrease in the total insulin that can be extracted from

the pancreas. These pathological data suggest that the defect may involve the production of insulin and the regeneration of islet cells, as well as the secretion of the hormone. It is interesting to hypothesize that these defects may have a common and interdependent origin, in the context of an altered glucose receptor mechanism in the diabetics' beta cells. Such an alteration could possibly contribute to the impaired renewal of islet tissue through failure to adequately stimulate cell division, for there is a suggestion that hyperglycemia may play a role in stimulating mitotic activity in the islets. In addition, this failure to respond normally to glucose could lead to a decrease in insulin biosynthesis and storage, because the glucose concentration is known to be a potent stimulus for this process. Finally, the failure of an adequate mechansim to monitor the extracellular glucose concentration would, of course, result in impairment of insulin secretion.

Although it is possible that the beta cell defect may affect only the efferent component of the insulin release mechanism, one would anticipate that the cellular stores of insulin would not only be preserved, but might be even greater than normal under these conditions. One might anticipate also that islet cell regenerative activity would lead to islet cell hyperplasia and cell proliferation. This situation has been found in the diabetic spiny mouse (Stauffacher et al., 1970), where there is a great increase in total islet tissue mass and the beta cells contain numerous secretion granules and large quantities of insulin. Recent evidence has indicated that these animals have an intrinsic defect in their secretory mechanism, probably involving the microtubular-microfilamentous system.

While the concept of a genetically determined intrinsic defect in the beta cells of most diabetics is an attractive working hypothesis, other factors, of largely environmental origin, merit further consideration. Recent studies of the inheritance pattern of diabetics and its incidence, particularly in identical twins (Tatersall and Pyke, 1972) strongly suggest that other causes for diabetes may exist and account for a significant fraction of the total number of patients. Studies of pancreatic pathology, particularly in juvenile diabetics, indicate the occurrence of a complex destructive lesion in the islets of Langerhans that may be due to extrinsic causes acting in a genetically favorable situation. Among such causes are two of particular interest and concern: autoimmunity and viral infection. These subjects will be dealt with in other testimony to the Commission.

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ISLET CELLS - INSULIN AND GLUCAGON SECRETION, AND INSULIN ACTION
D. F. Steiner, M.D.

Insulin Formation

Three basic research areas relating to the beta cell will be considered in this discussion: 1) Regulation of proinsulin and protein biosynthesis; 2) Structure and function of the plasma membrane; 3) Regulation of cell division and gene expression.

1. Regulation of Protein Synthesis – During the past few years progress has been made in understanding the mechanism of biosynthesis of insulin via its precursor form, proinsulin. The precursors have been isolated and characterized in several species, their amino acid sequences have been determined and work is progressing to achieve a better understanding of the three-dimensional structure of proinsulin in relation to that of insulin. All of these studies have enhanced our knowledge of beta cell function and also have provided insights into insulin action, insulin metabolism in the body, potential synthetic routes to new insulin preparations and new clinical and diagnostic methods for following and studying diabetics. It is natural to expect that further progress in this and related areas of basic research on islets will lead to further theoretically and practically useful concepts. Recent evidence indicates the participation of yet another precursor form in the biosynthesis of many secreted proteins. These are the so-called pre-secretory forms which have amino terminal extensions of 20-30 residues. These are best studied by translation of the appropriate messenger RNAs in suitable cell-free systems since cleavage of the precursor region occurs with great rapidity in the intact cell. Evidence for the existence of a preproinsulin has now been reported from several laboratories, and we have been able to confirm these findings using messenger RNA preparations from rat islets translated in wheat germ systems. The function of the pre-secretory protein seems to be to signal that the peptide is to be transferred across the membrane of the endoplasmic reticulum ultimately via the Golgi apparatus into secretory granules. The fate of the free "prepeptide" after its cleavage from proinsulin is not yet known but it may also be an ultimate secretory product of the beta cell which may have interesting and useful properties.

The regulation of insulin biosynthesis is not understood although work in our laboratory, as well as that of A. Permutt in St. Louis and others, has suggested that glucose stimulates insulin biosynthesis by increasing the rate of translation of pre-existing messenger RNA, and only after longer intervals does it appear to increase the production of new messenger RNA. The mechanism of translational control in animal cells is poorly understood. The recent exciting discovery by Shatkin and coworkers of the chemical "capping" of messenger RNA suggests a possible mechanism for regulating the translation of animal cell RNA.

These workers have reported the occurrence of 7-methylguanosine to the 5'
end of a wide variety of animal cell messenger RNAs. Moreover, the
removal or failure of addition of the guanosyl group or its methylation
prevent the translation of the messenger RNA in various in vitro systems,
such as the wheat germ ribosomal system. Little is known about the
possible participation of reversible methylation in the regulation of the
functions of nucleic acids or, for that matter, of proteins and enzymes.
Much further work in this area needs to be done and may shed light on
important questions related to insulin production and perhaps even to
insulin action.

2. The Structure and Functions of the Islet Plasma Membranes -
Although many theories abound regarding the mechanisms which regulate the
secretion of insulin and many of these implicate the beta cell membrane
as an important control point, almost no work has been done to isolate
and characterize plasma membranes from islet cells or beta cells. Work
on membranes in general has progressed in recent years such that a much
fuller understanding of the structure of the lipid bilayer, the assymetry
of its lipid composition and the arrangement of proteins within the
bilayer has become available. The Singer-Nicolson fluid-mosaic model is
of particular relevance since it appears to provide a sound theoretical
framework within which many membrane-associated phenomena can begin to be
understood. During the past year, Dr. Oke Lernmark, a Visiting Professor
in the Department of Biochemistry and the Diabetes-Endocrinology Center,
has begun work in this important area. Methods have been developed for
isolating the plasma membrane and it has been characterized in terms of
its content of marker enzymes such as 5'-nucleotidase, adenylate cyclase,
sodium-potassium-dependent ATPase, certain proteases and also by means of
electron microscopy and SDS-polyacrylamide gel electrophoresis. The
availability of such preparations should make it possible to further
examine the concept of a glucoreceptor as a membrane-localized component
and, in addition, it should become possible to study other hormone and
metabolite receptors, antigenic components, histocompatability sites and
viral receptors within these purified membranes. These studies should
help us to gain a better understanding of the possible unique suscepti-
bilities of beta cells to certain viral infections and autoimmune pro-
cesses. This is an area in which much further effort needs to be directed
and it must largely be directed at a highly fundamental level. Continued
studies of insulin secretion and its regulation by various agents and the
effects of various modifiers are, of course, of interest, but often provide
information that cannot be adequately interpreted without more detailed
knowledge of the chemical processes that are involved.

3. The Regulation of Gene Expression and Cell Division in the Beta
Cell - Our knowledge of the mechanisms which regulate the regeneration of
beta cells is rudimentary at best. Important progress has been made in
many laboratories in recent years with the growing interest in tissue
culture of normal islets and islet cell tumors. With the advent of these
techniques, it should be increasingly possible to study the interplay of
factors which regulate the synthesis of DNA and mitosis in the beta cells
under highly controlled conditions. The availability of a beta cell line

which would grow in vitro for long periods would not only enable the production of insulin in large amounts through fermentation-type procedures, but it would also facilitate studies on the effects of viral infection, autoimmune phenomena, toxic agents and endocrine regulation of the beta cells and their reproduction. It also will become possible, when beta cell lines are available, to study the chromosomal localization of important genes such as those coding for insulin, glucoreceptors, amino acid receptors and other proteins unique to the beta cells which may be altered in the beta cells of individuals predisposed to develop diabetes. In order to achieve these goals, much additional work will be required to perfect tissue culture methods and to develop new methods for separating the various cell populations of the islets into beta, alpha$_1$, alpha$_2$, and delta cells, etc., and to develop methods for stimulating and regulating their replication and function in vitro.

Progress in this area will undoubtedly depend on progress in the science of tissue culture in general, just as progress in the other areas described above will depend very heavily on progress in membrane biochemistry and on basic studies of mechanisms of protein biosynthesis in animal cells. It is therefore of considerable importance to encourage the support of fundamental and original or novel approaches to studies of islet cells, as well as to promote research in those areas of basic science that are most likely to be fruitful for further studies on the islets of Langerhans. These include basic membrane and nuclear biochemistry, cell biology, molecular biology and molecular genetics, with particular emphasis on the areas cited above. But clearly, studies on viruses, immunology, cell-cell interaction, cell fusion and many other areas also will ultimately become relevant and important to the search for better treatment and, hopefully, effective prevention and cure of diabetes.

GLUCAGON AND DIABETES MELLITUS

ROGER UNGER, M.D.

The islets of Langerhans regulate the distribution and concentration of glucose, the disposition of free fatty acids and ketones, and the anabolic or catabolic fate of amino acids. The finely controlled secretion of the opposing hormones, insulin and glucagon, is a process required to achieve the normal metabolic adjustments of the organism to changes in fuel demand and supply. The primary obligatory influence upon the a and B-cells is the arterial glucose level. This must require a finely developed glucose sensing capacity that directs the secretory events in these two cells.

In diabetes mellitus, there is a breakdown at some point between the sensing of glycemic change and the extrusion of the secretory product in both these cells. The B-cell defect, causing a relative or absolute deficiency of insulin, casues in its most subtle stages, a delay in the ability to utilize exogenous glucose and, in its more advanced forms, marked impairment of glucose utilization, increased lipolysis and breakdown of protein.

However, diabetes is also characterized by an a-cell defect, causing a relative or absolute excess of glucagon, responsible for increased hepatic glucose production from glycogenolysis and gluconeogenesis, thus wasting amino acid nitrogen that would otherwise be available for protein biosynthesis, and setting the liver in a ketogenic mode so that if the insulin lack is severe enough to cause hyperlipolysis, massive quantities of ketones will be produced.

The availability, for the first time, of a potent glucagon-suppressing agent, somatostatin, has revealed the magnitude of glucagon's role in all forms of diabetes. Glucagon suppression can prevent development of endogenous hyperglycemia and ketosis in the total absence of insulin, including that which develops after total pancreatectomy when extrapancreatic a-cells produce hyperglucagonemia.

The importance of glucagon in the metabolic abnormalities of human diabetes is clear. It is not clear whether the a-cell defect is independent of insulin lack, a separate, perhaps even primary, component of the disease. Although infusion of insulin, even in low doses, will reduce plasma glucagon in fasting diabetics, only large doses bring the plasma glucagon to levels as low as those reached by hyperglycemic nondiabetics with small insulin doses. Moreover, in hyperinsulinemic adult-type diabetic Pima Indians, the response to arginine is just as exaggerated as in hypoinsulinemic adult-type diabetic Pimas, and significantly greater than that of nondiabetic Pimas with intermediate insulin levels. In first de-

gree nondiabetic relatives of diabetics, nondiabetic identical twins of diabetics, diminished suppressibility by oral glucose is reported. Finally, an exaggerated glucagon response to arginine has been reported in nondiabetic offspring of two diabetic parents at a time when insulin levels were perfectly normal. These reports suggest that a-cell function may be abnormal before overt B-cell disease is apparent.

In established adult-type diabetics, the hyposuppressibility to a carbohydrate meal could not be corrected by supraphysiologic quantities of insulin, suggesting that, while insulin can suppress plasma glucagon in all forms of diabetes, insulin deficiency is not the cause of the a-cell dysfunction.

In juvenile-type diabetics, in whom blood glucose and glucagon were measured at 2-hour intervals for six days during which an attempt was made to achieve optimal regulation by insulin administration, from 90 to 210 U per day were required to correct the hyperglycemia; in some patients, both glucose and glucagon levels were normalized by the large doses of insulin, but in others, normalization could not be achieved even by very high insulin doses. Yet, somatostatin, when given together with insulin, dramatically suppresses both the glucagon and the glucose concentration and even prevents postprandial hyperglucagonemia and hyperglycemia, which insulin alone does not prevent.

The conclusion from these observations is that insulin therapy does not restore to normal the alpha cell function in the majority of diabetic patients; but, when glucagon is suppressed to or below normal, a remarkable disappearance of hyperglycemia, even postprandial hyperglycemia results.

Conventional forms of therapy of diabetics have been disappointing in terms of ability to normalize glycemia and to prevent diabetic complications. The need of improved treatment of diabetes is undisputed. Therapeutic glucagon suppression would appear to be an approach deserving of careful study in diabetics and perhaps in prediabetics as well.

OBESITY AND DIABETES-LIKE SYNDROMES IN MICE

D. L. Coleman, Ph.D.

Mutations at three loci, obese (ob), diabetes (db), and agouti (A) cause obesity and diabetes-like syndromes in mice. Diabetes and obese, recessive mutations located in chromosomes four and six respectively, have been studied more extensively than the dominant alleles (yellow, A^y; viable yellow, A^{vy}; and intermediate yellow, A^{iy}) at the agouti locus in chromosome two. The mutation, diabetes (db), occurred in the C57BL/KsJ strain and on this background is characterized by obesity, hyperphagia, and a severe diabetes with marked hyperglycemia, temporarily elevated plasma insulin concentrations, typical degenerative changes in the islets of Langerhans, and a shortened lifespan. The obese (ob) mutation occurred in a noninbred stock but was later established and has been maintained in the C57BL/6J strain. C57BL/6J-obese mice are characterized by marked obesity, hyperphagia, transient hyperglycemia and markedly elevated plasma insulin concentrations associated with marked hypertrophy of the islets and increased proliferative capacity of the beta cells. Studies of the effects of these two inbred backgrounds on the expressions of the diabetes and obese mutations have revealed that the two genes, if acting in the same strain, exhibit identical syndromes. Both diabetes and obese mice of the C57BL/KsJ strains have the severe diabetic conditions characterized by islet atrophy, whereas both mutations on the C57BL/6J strain have the mild diabetic condition characterized by islet hypertrophy and hyperplasia of the beta cells. The metabolic disorder produced by each mutation is associated with the capacity of the islets to respond to an increased demand for insulin. The islet response, atrophy or hypertrophy, appears to be due to modifiers in the genetic background rather than to the specific action of the particular gene. The yellow alleles have not been established on the C57BL/KsJ background but on the C57BL/6J background they show islet hypertrophy and very mild diabetes. The markedly different diabetic syndromes resulting when obese and diabetes are on different inbred backgrounds emphasize the importance of strict genetic control in studies with obese-hyperglycemic mutants.

Having obese and diabetes on the same inbred backgrounds has permitted parabiosis which requires histocompatible stocks. Parabiosis of diabetes (db/db) with normal mice resulted in the death of the normal mouse, apparently of starvation, within three to four weeks. Our interpretation of this finding is that the diabetes partner produces but does not respond to a satiety factor that prevents overeating. In parabiosis this factor crosses into the circulation of the normal partner where it acts on its satiety center to inhibit eating, with subsequent starvation and death. Parabiosis of two diabetes mice is not lethal to either

because both have defective satiety centers. When obese (ob/ob) mice were parabiosed with diabetes (db/db) mice, the obese partner lost weight and died of starvation while no abnormal changes were observed in the diabetes partner. This suggests that obese mice are like normal mice and have normal satiety centers responsive to satiety factor. In unions of obese with normal mice, both partners survive suggesting that the obese partner does not produce sufficient satiety factor to turn off the normal partner's eating drive. However obese mice in such pairs eat less and gain weight less rapidly than obese mice paired with obese mice. This observation suggests that the normal partner provides a humoral factor that regulates food consumption and rate of weight gain in the obese partner. We postulate that the obese mouse is unable to produce sufficient satiety factor to regulate its food consumption, whereas the diabetes mouse produces satiety factor, but cannot respond to it because of a defective satiety center. This would explain the identical obese-hyperglycemic-syndromes produced by these two unrelated genes when they are acting in identical genetic backgrounds.

Inbred strains of mice carrying various single gene mutations causing diabetes or diabetes-like syndromes offer many advantages to researchers. Appropriate matings can be made that will produce predictable numbers of unaffected and diabetic mice, all of which are of the same strain differing only by a single gene, a feature that greatly facilitates interpretation of biochemical and morphological results. Having several single genes that can cause identical diabetic conditions in the mouse could greatly aid the unravelling of the nature and types of metabolic defects that can lead to diabetic states in man. Also, an understanding of the mode of action of the modifying genes in the various inbred strains that change the course of the disease from a severe juvenile type to a mild maturity onset type would be an important contribution to the understanding of human diabetes variants. That these single genes are maintained on inbred strains which are identical in every respect not only permits an abundant supply of known identical controls differing only with respect to the mutant gene in question, but also permits studies such as parabiosis (discussed previously) as well as organ and tissue transplantation (especially the islets of Langerhans) without concern for tissue incompatibility between the normal and mutant mice. Such transplantation studies with various organs should establish or rule out whether the primary lesion involves the particular transplanted tissue. Finally, it is possible that the mutant gene interacts not only with the host genome but is influenced by the presence of, or susceptibility to, viral agents. Thus the BL/6 mouse may respond with islet hypertrophy, beta cell hyperplasia and mild diabetes because it is immune to the action of endogenous viruses whereas the BL/Ks mouse is sensitive to the virus and the combination of the gene plus virus may lead to islet atrophy and severe diabetes. Again, the inbred mouse model makes an excellent tool to test these possibilities.

Recommendations

There should be more support to maintain the natural and genetic models of diabetes. Presently the only means of support available is via the Research Grant system which judges applications primarily on scientific merit by suitable Study Sections. Many times the proposal submitted has little or no scientific merit with regard to the research plan and overall procedure. These proposals are rejected or go unfunded because of low priority. However in most cases the model described sounds intriguing and most Study Section members feel that it should be preserved for the entire scientific community to evaluate. Therefore we need another mechanism to defray expenses incurred in maintaining animal models at least in the period before the model has been fully evaluated. A possible mechanism would be that all Research Proposals dealing with models be sent not to the Study Section immediately but to another group for evaluation of the relevance of the model and the proportion of the budget required to maintain the colony. If appropriate, the animal maintenance portion of the application could be recommended for funding and the scientific merit deferred to Study Section action.

POSSIBLE ROLE OF VIRUSES IN THE ETIOLOGY
OF DIABETES MELLITUS

John E. Craighead, M.D.

Annotations in the literature and epidemiological observations long have suggested that viruses may play a role in the etiology of juvenile-type, insulin-dependent diabetes mellitus in man. Many features of the disease are consistent with this hypothesis. Juvenile-type diabetes is abrupt in onset and new cases appear to occur more commonly in some seasons, or in some years, than in others. Pathologically, the islets of recently affected individuals often exhibit an inflammatory infiltrate, and the beta cells in the pancreatic islets are substantially reduced.

Although considerable interest has focused on mumps, recent observations strongly suggest that diabetes is associated with infection by coxsackievirus group B, type 4. Both of these viruses are known to involve pancreatic tissue in man and cause lesions of the acinar and insular cells. Rubella virus and cytomegalovirus also have been implicated although the evidence is more circumstantial. On the basis of the existing evidence it seems reasonable to suggest that the insular tissue of the pancreas is occasionally affected during the course of systemic viral infections. If so, constitutional and genetic factors may influence the susceptibility of the beta cell and the extent of the damage which occurs.

Recent experimental evidence supports this concept. Two models of viral insulitis have been described, one caused by a small RNA containing virus -- EMC, and the second by a member of the DNA containing herpesvirus group -- cytomegalovirus. EMC virus is similar to the coxsackieviruses of man; cytomegalovirus is a chronic viral infection, particularly in humans with modified immunologic responsiveness.

Mice infected with EMC virus develop hyperglycemia and hypoinsulinemia shortly after inoculation. At this time the beta cells are degranulated and the pancreatic insulin content is reduced. Diabetes persists in these animals for varying periods of time. Some mice exhibit a chronic debilitating disease and die with ketoacidosis three to six months after inoculation. The insular mass in these animals is reduced substantially and little insulin is present in the pancreas. Other animals are chronically hyperglycemic and hyperphagic. They survive indefinitely although pathologic alterations are frequently observed in the pancreatic tissue. A number of chronically diabetic

animals become normoglycemic during convalescence. In these mice regeneration of beta cells and metaplasia of acinar cells appears to occur.

Genetic factors influence the occurrence of diabetes in mice. Some inbred strains are highly susceptible whereas others are resistant. Classical genetic studies strongly suggest that the heritable influences are polygenic. Constitutional factors also play a role. Obesity and steroid hormones increase the susceptibility of the pancreatic insular tissue.

Cytomegalovirus infects the pancreatic insular tissue of immuno-suppressed mice. Although these animals have not been shown as yet to develop diabetes, it seems likely that this disease could develop under some circumstances.

Immunologic factors may contribute to the chronicity of disease in virus infected animals and man. Necrosis of beta cells may sensitize so that immunoglobulins react with otherwise normal insular cells. Alternatively, viruses such as cytomegalovirus cause the production of neoantigens on the cell surface. One might envision the occurrence of a cell mediated immune response damaging beta cells. These considerations are speculative.

SUGGESTED AREAS FOR FURTHER STUDY IN THE EPIDEMIOLOGY AND GENETICS OF JUVENILE-TYPE DIABETES MELLITUS

John E. Craighead, M.D.

Epidemiology

1. Population Surveillance. Selected representative population groups, on a national or world-wide scale, should be identified to assess prospectively the occurrence of new cases of juvenile-type diabetes mellitus in relation to: (a) seasonal trends in onset, (b) year-to-year variations in the numbers of new cases, (c) associations with environmental influences such as epidemics of mumps, rubella, influenza, or enteroviruses. Vaccine programs may also prove of interest since they conceivably could reduce the prevalence of disease, or as suggested by Sultz, increase it. The size and selection of the population groups under investigation will necessitate refined evaluation. Investigations of this type require close liaison with the population group under study, and careful monitoring of disease by various means of communication. Inasmuch as the nature of the study would be well defined, it could probably be carried out by a governmental agency such as the NCDC, or by contract.

2. Early Case and Cluster Identification. Should infectious agents play a direct or contributory role in the pathogenesis of the disease, it will be necessary to identify these agents and establish the nature of the infectious process. Inasmuch as the interval from infection to the onset of metabolic disease may be extended, a few opportunities to identify the infectious agent may arise. Accordingly, a sizable population must be maintained under surveillance and an effective means of rapid communication and patient evaluation developed.

The nucleus of such a surveillance system exists at the NCDC at present. As you know, the epidemiologic intelligence officer (EIS) is available on a world-wide basis to investigate outbreaks of disease. Moreover, NCDC maintains close liaison with State Public Health Departments. EIS officers stationed locally could investigate, by protocol, cases as they are reported. It would be difficult to envision such a program functioning satisfactorily using personnel from academic or commercial institutions.

Clusters of new cases of juvenile-type diabetes mellitus have been reported on a number of occasions. These reports remain largely anecdotal inasmuch as critical epidemiologic studies have not been undertaken. Clearly, a system should be developed to accomplish this goal. Because these hypothetical events would be expected to occur

rarely, surveillance by NCDC would be the most appropriate approach.

3. Cell Membrane Marker Antigens in Epidemiologic Surveys. Identification of antigenic markers such as the HL-A and LD transplantation antigens should be carried out in a significant population of diabetics with appropriate controls. Studies of this type should be incorporated into other epidemiologic investigations, since it would be desirable to accumulate information on seasonal trends, year-to-year variation and epidemiologic influences in relation to various antigenic markers on cell membranes.

4. Studies of Viral Infections Associated with Various Cell Membrane Marker Antigens. Considerable circumstantial and experimental evidence suggests that specific tissue types may be associated with immunologic responsiveness and disease susceptibility. For a number of obvious reasons, it is difficult to accumulate supportive information in man without a carefully designed protocol and adequate laboratory backup. With regard to the possible role of viruses in the pathogenesis of juvenile-type diabetes, it would be important to determine whether or not the following differ in individuals with various tissue types: (a) humoral or cellular immunologic responsiveness to virus infections, (b) increased susceptibility to common virus infections, (c) differences between individuals with various tissue types in glucose tolerance and insulin responsiveness.

5. Retrospective Population Surveys. As you know, epidemiologic and virologic investigations currently are being carried out to determine a possible association between virus infections and the juvenile form of the disease. Retrospective studies are now underway in Denmark, Great Britain, and the United States. In Denmark and in this country, tissue typing is being done in conjunction with virus serologic work.

It is too early to assess the usefulness of investigations of this type in defining possible etiology agents that play a pathogenetic role in diabetes mellitus. There are important theoretical objections to retrospective surveys which may invalidate this approach.

An alternate means for addressing this problem is the prospective investigation in which communities are monitored over extended periods of time in a systematic fashion. Since this approach would necessitate maintaining several large populations (several hundred thousand) under long-term intensive surveillance, I believe they would prove impractical and inordinately expensive. Accordingly, despite its shortcomings, the retrospective survey seems most appropriate at this time.

Viral Experimental Models

The EMC virus model of diabetes mellitus is the outgrowth of a serendipitous observation. It seems that other viruses of the same or different class might exhibit characteristics similar to the "M" variant of EMC virus. Appropriate systematic studies to determine the validity of this assumption have not been carried out. Thus, we do not know at present whether the unique beta cell tropism of the "M" variant of EMC virus is limited to this agent alone, or is a characteristic of a number of different viruses or virus strains. Pathologic studies in man and experiments in animals indicate that cytomegalovirus may be one such agent. Intensive investigations in the future should be carried out to answer this question.

Studies with viruses have been largely confined to experimental animals although some workers have explored the infectivity of the "M" variant for beta cells in isolated islet systems and monolayers of beta cells. The latter investigations should be emphasized and supported for they will permit evaluation of the complex pathogenetic factor that influence cell susceptibility and the development of the lesion. Based on experimental work we have good reason to believe that hormonal and metabolic factors in the animal as a whole, as well as the metabolic state of the beta cells, are critical. Considerable additional study is indicated.

Inasmuch as the "M" variant of EMC virus appears to preferentially infect beta cells, one must assume that the membranes of these cells possess specific receptors which differ from receptors for closely related viral agents. The presence or density of receptors probably are influenced by the genetic characteristics of the susceptible or unsusceptible animal as appears to be the case with alloxan and other chemical diabetigenic agents. This problem merits careful evaluation in well controlled systems.

Although cell receptors may affect the occurrence or severity of an infection, other genetically determined factors external to the individual beta cell may be critical. For example, immunopathologic considerations demand a careful assessment. It is likely that immuno-logic mechanisms may play a role in accentuating the severity of a virus-induced lesion of the beta cells or lead to a chronic or progressive process. Viruses which replicate in beta cells, for example EMC and cytomegalovirus, multiply by quite differing mechanisms and therefore would influence the immunologic response of the host in differing ways. These questions can be subject to evaluation at the present time and should be pursued.

DIABETES IN THE SPONTANEOUSLY
DIABETIC CHINESE HAMSTER

William E. Dulin, Ph.D.

This discussion will address three important questions:

1. Why do we need animal models for diabetes?

2. Why is the Chinese hamster a good model?

3. What research remains?

1. <u>Why do we need animal models for diabetes</u>?

The problems of diabetes are to halt progression or reverse complica-
tions in the diagnosed diabetic, and to prevent these changes from
occurring. To solve these problems, we must determine who is at risk.
To do so requires detection of genetic diabetics by some marker other
than blood sugar since blood sugar is a late manifestation and is
influenced by innumerable factors.

Blood sugar changes and probably changes in tissues leading to
complications are far removed from the site of gene action. Since
diabetes is an extremely heterogeneous disease, diabetics with different
genotypes can be expected to have different basic genetic defects and
consequently all diabetics cannot be treated as a statistically uniform
group.

Attempts to discover the genetic markers in man will take many years
to determine even if we use the correct marker as it requires consider-
able time to proceed from the prediabetic to the diabetic state. All
diabetics do not develop complications so endpoints are needed to
determine who will. Many of the clinical studies have used different
endpoints, involved relatively small numbers of patients, used different
criteria for patient selection, and data from a heterogeneous group of
syndromes have been grouped statistically. Therefore, if we want to
solve the problem of diabetes in man, we need specific markers which have
a high probability of being directly related to gene action. Finding
these markers in the more easily studied animal models and using the
information as guidelines for more complex human studies provides the
highest probability of success.

2. Why is the Chinese hamster a good model?

To answer this question, it is important to describe or present knowledge of diabetes in this species and compare it with diabetes in man.

Pancreatic insulin and the ability to synthesize and secrete insulin is depressed in the diabetic Chinese hamster.

Inheritance of diabetes in the Chinese hamster probably involves four pairs of genes with diabetes resulting when two pairs of genes are homozygous recessive and ketosis resulting when three pairs of genes are homozygous recessive. Some inbred lines breed true for diabetes, but differ in ages of onset and severity, thus indicating genetic heterogeneity. Nondiabetic lines have been produced. Production of normal offspring from crossing lines which produce a high percentage of nondiabetics provides additional evidence of heterogeneity.

Prediabetic Chinese hamsters can be identified at birth in lines which breed true for diabetes or offspring from two ketotic diabetic animals. Availability of prediabetics provides a tool to search for gene controlled lesions before extensive metabolic changes create problems.

Normalization of dietary intake reduces severity or prevents diabetes and normalizes life span of genetic diabetic animals. Therefore, environmental modification can predictably affect the expression of the genetic mutations.

Considerable pathological changes have been observed in the diabetic hamster. The retina of some diabetics shows decreased mural cells, nerve cell degeneration and accumulation of PAS positive material. Diabetic neuropathy is evidence by segmental demyelination and remyelination of peripheral nerves, neurogenic bladder syndrome with alteration of nerve fibers and a degeneration of cholinergic terminals. Nephropathy has been evidence by PAS positive material in the glomeruli and glomerularsclerosis. The aorta has shown early changes of atherosclerosis, such as lipid accumulation, smooth muscle cells in the intima and calcium deposits surrounded by collagen fibers in the media.

These observations suggest that the diabetic Chinese hamster exhibits many genetic and metabolic characteristics associated with diabetes in man. Although these changes are frequently not as advanced as one finds in the long-term human diabetic, they are typical of the early changes.

Techniques have been developed for islet culture, beta cell isolation, ovarian transplantation and whole pancreatic transplantation. In

addition, many computer programs have been developed for data storage and analysis.

3. What research remains?

One of the principal problems hindering the research on the Chinese hamster is insufficient numbers of various types of animals. Significant progress will only be possible with additional breeding capability. Fertility problems in male and female diabetics require study in order to increase productivity. Ovarian transplantation may help circumvent some fertility problems and increase production of animals with specific genetic backgrounds. Doubling of the present colony should produce sufficient animals.

Increased effort must be made on the genetic studies designed to develop inbred lines with a single gene mutation and breeding schemes have been designed. Lines with single mutations will allow evaluation of biochemical and pathological changes which are controlled by each gene and specific recombination of the genes to determine the relative contributions of each mutation.

Studies on the function and morphology of alpha and beta cells from cell cultures and in vivo as well as studies on enzyme changes in organs which develop complications are needed.

Studies must be expanded to determine the relative contribution of genetics and environment on development of diabetes and the complications. Ovarian transplants will allow exposure of different genetic backgrounds to different intrauterine environments. Implantation of islets, beta cells, and total pancreatic transplants will enable us to separate the relative importance of genetic and environmental factors in phenotypic expression of the diabetic genes and to determine if genetic or bio-chemical changes of diabetics are detrimental to normal beta cells.

Intervention studies on prediabetics should be carried out to determine the role of dietary components, insulin therapy and other rational changes on the development of diabetes and its complications.

Extension of the pathology studies to determine the earliest changes in the nervous system, GI tract, reproductive tract, kidney and eye is important. Correlation of severity and duration of metabolic changes with development of pathological changes should be expanded in order to determine if there is a correlation of the metabolic changes with these adverse effects of this disease syndrome.

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RECOMMENDATIONS FOR STUDIES ON THE
GENETICS OF HUMAN DIABETES

Stefan Fajans, M.D.

Listed below are a number of areas in which further studies are needed.

- To define, and differentiate between, familial incidence of diabetes in patients with classical juvenile-onset type diabetes (JOD) and in patients with maturity-onset type diabetes of the young (MODY), and to establish more firmly a difference in the pattern of inheritance between these two types of diabetes. Families in which both types of diabetes are found should be studied particularly carefully.

- To examine for possible heterogeneity among JODs and MODYs in terms of inheritance, insulin secretion, C-peptide, HL-A or LD typing, viral antibodies, and cell mediated antibodies. Look particularly among MODY for autosomal dominant vs. other types of inheritance.

- To carry out further studies of insulin responses to glucose among MODY in a longitudinal fashion to learn about the prognostic significance of low insulin responses and high insulin responses. In those with high insulin responses, study for possible variations in insulin moieties in plasma and the activity of target cell receptors for insulin to clarify the cause and nature of the hyperinsulinemia.

- To establish among the propositi of patients with JOD and MOD, but late onset of diabetes (fifth and sixth decade), any differences in (a) inheritance, (b) insulin responses, (c) HL-A or LD typing, (d) virus antibodies, and (e) cellular antibodies.

- In JODs with negative HL-A or LD typing look for other types, as yet undetected, of histocompatibility markers.

- In nondiabetic family members of JOD (siblings) with positive or negative histocompatibility typing, perform prospective studies in terms of virus antibodies, cell mediated antibodies as described by McLaren, insulin secretion to identify factors determining susceptibility or playing role in pathogenesis. Genetic counseling.

- Genetic counseling in MODY. Preventative measures such as diet or oral agent in prospective longitudinal controlled studies.

- In relation to the third above, one might use large domestic animals with diabetes in a search for possible abnormal insulin molecules.

- Encourage twin studies.

- Look for correlation of histocompatibility types with vascular complications in long term JOD.

IN VITRO REPLICATIVE CAPACITY OF CELLS FROM SUBJECTS WITH THE DIABETIC GENOTYPE

Samuel Goldstein, M.D.

The use of tissue culture enables us to distinguish between genetic and environmental influences on phenotypic expression. It also permits the study of cells from known individuals with specific predispositions to genetic-metabolic disease. Cultured skin fibroblasts derived from subjects with genetic prediabetes mellitus and overt diabetes have a reduced replicative capacity compared to normal controls. Growth is also reduced in cultures derived from individuals with progeria and Werner's syndrome, both of which feature insulin-resistant diabetes, accelerated againg and premature death. The replicative capacity of cultured cells is decreased in normal populations as a function of age but individuals who maintain normal glucose tolerance, particularly beyond middle age, appear to perform better than the population at large, perhaps on the basis of Darwinian selection. Present and future studies are needed and/or in progress to further delineate the relationship between glucose tolerance, physiological aging and the replicative capacity of cultured cells.

Altered expression of HL-A antigens occurs in progeria and Werner's fibroblasts but only in a fraction of clones of normal cells undergoing aging. Interaction of aged cells with polymerizing fibrin to form a fibrin clot and eventual retraction of the clot is also impaired at the same time as the appearance of increased amounts of a thromboplastic substance. Additionally, heat-labile enzymes comprise a larger fraction of the total enzyme complement in aging cells while preliminary evidence suggests that insulin receptors are reduced in number and possibly affinity in progeria and perhaps normally aging fibroblasts. Other studies demonstrate that the de novo synthesis of triglyceride and cholesterol ester is increased in diabetic fibroblasts.

In total these observations indicate that aged cells contain a diversity of abnormal gene products. These may contribute to a number of age-dependent disease processes such as impaired wound healing, athero-thrombotic disease, insulin resistance, impairment of self-recognition

(auto-immunity) and abnormal lipid synthesis. This system should be valuable in exploring the pathogenesis of the diabetic state as well as its relationship to biological aging and the attendant premature appearance of age-dependent pathology.

SUMMARY OF PRESENTATION TO THE NATIONAL
COMMISSION ON DIABETES

Jørn Nerup, M.D., PhD.

Recently we described the association between HL-A 8 and W15 and
insulin-dependent diabetes mellitus (Lancet 2:864, 1974). The clinical
significance of this association is unknown but preliminary studies
have shown:

1. The relative risk (RR) of insulin-dependent diabetes for
   carriers of HL-A 8 and W15 is 2.3 and 2.2 respectively. RR of
   maturity (non-insulin-dependent) diabetes was not increased.

2. RRs for HL-A 8 and W15 heterozygotes and homozygotes were
   identical, i.e., no "gene dose effect" exists.

3. RR of insulin-dependent diabetes for HL-A 8 + W15 carriers was
   the sum of the individual RRs of HL-A 8 and W15.

4. The prevalence of diabetes mellitus among siblings of diabetics
   with HL-A 8, W15 and 8+W15 is 10, 11, and 20 percent
   respectively corresponding to the calculated RRs.

5. Early insulin response (IVGTT) in 1. degree relatives
   (siblings) to HL-A and W15 positive diabetics was decreased in
   nondiabetic HL-A 8 and W15 carriers.

6. Proliferative retinopathy was predominantly found in HL-A and
   W15 positive diabetics.

Thus the HL-A factors seem to be of some significance for the develop-
ment and course of the disease.

Further investigations revealed:

1. The LD-types 8a and W15a are more strongly associated with JDM
   than the SD-types 8 and W15. LD-8a and/or W15 occurred in 80
   percent of the patients compared to 25 percent in the controls.
   Relative risks for LD-8a and W15a: 6.4 and 3.7 respectively.

2. Islet cell antibody (ICA) and antipancreatic, cell-mediated
   immunity (APCI) was demonstrated in 55 and 34 percent of the
   patients with JDM of short duration.

3. ICA and/or APCI was present in 73 percent of the patients, showing that autoimmunity is a common feature of JDM. Ninety percent of the HL-A 8 positive diabetics presented autoimmune phenomena.

4. ICA was found in 75 percent of the LD-8a positive diabetes compared to 36 percent of the LD-8a negatives.

5. Antibodies to Cox B_4 virus were predominantly found in ICA positive sera.

These findings link together the genetic markets of JDM with auto-immunity and viral infections, thereby supporting the hypothesis, that the inherited susceptibility to develop juvenile diabetes mellitus (JDM) is conferred by LD-8a and W15a associated immune-response genes responsible for a defective T-lymphocyte response to certain virus, leading to B-cell destruction directly or through the triggering of autoimmune reactions.

Recommendations

In relation to our own lines of investigation:

1. A prospective study of recently diagnosed juvenile diabetics and proper controls could reveal the correlations between HL-A types (especially the LD-types) virus and autoimmunity, thereby giving important information with regard to the above mentioned hypothesis.

    If this hypothesis is correct, future research could be directed towards prevention (immune stimulation and immunization) of juvenile diabetes.

    As far as I know, studies are in progress in the United States, Great Britain, and Denmark.

2. Family studies and segregation analyses of HL-A types in diabetic families could give very important results in relation to genetic counseling of diabetics.

3. Studies of HL-A types in diabetic twin pairs would be of importance as a supplement to (2).

    The population of Great Britain and Denmark would be suitable in relation to (2) and (3) (high population density, ethnically well-defined, twin registers existing).

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Since these topics were the only ones presented at the meeting with direct relations to etiology and pathogenesis of human juvenile diabetes, it is possibly not too unfair to propose to the commission to consider the possibility of economic support to the British and Danish groups.

4. Studies on the B-cell cytotoxicity of islet cell antibodies and sensitized diabetic lymphocytes _in vitro_ are obviously of the greatest interest.

    A joint study between Dr. Chick of the Joslin Clinic and our group could easily be undertaken. The costs would be relatively small, but studies on the B-cell killing effects of diabetic lymphocytes would necessitate for some months, that the two groups work together in the same laboratory, preferably in Copenhagen.

5. I see little need to use large sums to create new tissue typing laboratories to evaluate in depth the importance of the association between HL-A and juvenile diabetes. With economic support the existing capacity of a few labs could be expanded during a one to two year period to do the job.

6. The Canadian Wistar rats should by all means be saved. They possibly represent the only model of human juvenile diabetes with respect to genetics and infection.

RESEARCH IN THE AREA OF VIRAL
INFECTIONS AND DIABETES

Abner Louis Notkins, M.D.

Since the late 1800s, there have been numerous reports showing a temporal relationship between the onset of viral infections and the development of diabetes. A variety of viruses have been implicated in the etiology of diabetes with mumps being the most popular candidate. Since, however, the incidence of both mumps and diabetes is high, it is possible that the relationship between the two might be fortuitous. Recently, it has been suggested that Coxsackie viruses also might produce diabetes. The neutralizing antibody titer to Coxsackie B4 was found to be higher in newly diagnosed diabetic patients as compared to nondiabetic controls. The antibody titer to a variety of other viruses, including mumps, was not significantly different. Although provocative, a number of other factors might account for these relationships and proof that viruses cause diabetes in man is still lacking.

Evidence that viruses can produce diabetes in animals is more convincing. The M variant of encephalomyocarditis virus infects and destroys beta cells producing a diabetes-like syndrome in mice characterized by hyperglycemia, glycosuria, polydipsia, polyphagia and hypoinsulinemia. The secondary manifestations of human diabetes have not yet been convincingly demonstrated in the animal studies.

A number of factors influence the development of diabetes in mice. The most important of these is the tropism of particular viruses for the beta cells of the pancreas; genetically determined differences in the susceptibility of the host; and the influence of environmental factors on the initiation and expression of viral-induced diabetes.

On the basis of the available information, research in the following areas is indicated.

1. Demonstration that viruses can produce diabetes in animals other than mice, including subhuman primates;

2. Isolation of viruses from diabetic patients, especially those with acute onset juvenile-type diabetes;

3. Identification of the genetically determined factors that are responsible for the development of viral-induced diabetes;

4. Establishment of good _in vitro_ techniques for the cultivation of beta cells;

5. Seroepidemiologic studies showing a relationship between
   viral infections, HLA type and the development of diabetes.

GENETICS IN THE ETIOLOGY OF DIABETES

David Pyke, M.D.

The ultimate purpose of the study of the genetics of diabetes is to prevent, delay, or ameliorate the disease.

There is good evidence that diabetes is, at least in part, genetic. (1) Diabetics give a family history of the disease more often than non-diabetics. (2) Some families show a striking incidence of diabetes. (3) Monozygotic twins show a higher concordance rate than dizygotic twins.

Nevertheless, there is also evidence that inheritance is not the only cause of diabetes. (1) There is no clear pattern of inheritance. (2) In many cases, there is no family history of diabetes. (3) The prevalence of diabetes in the population is relatively high for an inherited condition -- most inherited disorders, being biologically disadvantageous, are maintained in the population by mutation and therefore attain only a low prevalence. (4) Although monozygotic twins show a high concordance for diabetes, it never reaches 100 percent. (5) Diabetes may be due to nongenetic factors, such as obesity, steroid therapy, and parity.

There is doubt as to the mode of inheritance. The most popular theory has been that diabetes is inherited as an autosomal recessive character. The evidence for this was never very firm; the prevalence of diabetes among the offspring of two diabetic parents, which should be 100 percent if the disease is due to a recessive gene, is in fact about 5 percent (although higher figures are found when detailed testing is done).

Although the recessive gene theory is largely discredited, it still provides the basis of much research on "pre-diabetics" in whom minor metabolic and tissue changes are assumed to be the earliest manifestation of overt diabetes.

It seems more probable that diabetes is multifactorial in etiology and in genetic determination, i.e., that several factors -- some environmental, some genetic -- may lead to diabetes and that, even within the genetic group, the condition is heterogeneous. The reasons for saying this are (1) concordance rates in early-onset diabetic identical twins do not reach 100 percent and, according to present evidence, never will. Yet (2) among older-onset twins, all are concordant. Insofar as the twins can be taken as representative of diabetes in the general population, this suggests that there are at

least two types of diabetes -- an early-onset type, which is inherited in no more than 50 percent of cases, and of an older-onset type, which seems to be almost entirely genetic in origin. This is the reverse of what had previously been assumed -- young-onset cases having been thought to be more "genetic" than older. However, studies of histo-compatibility antigen frequencies show that, even in discordant pairs, genetic predisposition to diabetes exists.

Virus infection may, either directly or via the initiation of an autoimmune response, be an important factor in some early-onset cases. Studies are in progress on virus and autoantibody titers in the identical twins in an attempt to define factors which might account for the difference between the concordant and discordant pairs.

There are a large number of conditions in which diabetes is almost always associated with other disorders, such as diabetes insipidus, optic atrophy, etc., in which a pattern of recessive inheritance is certain. One type of diabetes has recently been defined which is unassociated with other disorders and is conspicuously mild and uncomplicated; this type is inherited in a dominant manner. It is probable that it is the milder forms and features of diabetes which are inherited and that the more acute and severe forms, although owing something to genetic predisposition, are predominantly exogenous in causation. Diabetes is not a single entity with a unitary cause, genetic or environmental. The present need is to define sub-groups in diabetes and to study genetic and environmental factors in their causation.

Finally, twin studies suggest that inheritance may influence not only the development of diabetes but also the type and severity of its complications.

SUMMARY AND RECOMMENDATIONS RESULTING FROM PRESENTATIONS
AND REFLECTIONS AT AND ON THE WORKSHOP CONCERNED WITH GENETIC
AND EXPERIMENTAL "MODELS" FOR DIABETES

Albert E. Renold, M.D.

A. BRIEF SUMMARY OF MAIN CONCLUSIONS OF WORK WITH "MODELS" SO FAR

1) The variety of animals, among them many laboratory rodents, with
a tendency to develop spontaneous hyperglycemia (and thus what we define
as diabetes) has already established that hyperglycemia, with or without
ketosis, may be the expression of a rather widely distributed metabolic
variant among multi-cellular organisms, certainly among mammals, probably
also among fish. It seems clear that these spontaneous syndromes may
result from more than one genetic anomaly; the mode of hereditary trans-
mission may vary as well.

2) Although in man, conclusion (1) is still questioned, at least by
some experts with much weight of tradition, the unmatched number of
observations on a very large number of individuals (more than ten thou-
sand tested twice monthly throughout life, i.e. an average life-span of
one to three years, and several inbred lines of Chinese hamsters (as
reported at this Workshop by Dr. W. Dulin) has established beyond rea-
sonable doubt, that in this species, at least, hyperglycemia, with or
without ketosis, is a clearly polygenic syndrome, involving at least
four pairs of alleles.

3) Similarly, the information accumulated on several well-defined
mouse mutants observed and bred at the Jackson Laboratories in Bar
Harbor, Maine, the first and still the principal pioneer in the field
of the search for mutants in mice, has served to establish the import-
ance, not only of a given mutant gene in itself, but also that of the
remainder of the genome to which it "belongs" or gets transferred.
Again, the result is a polygenic view of the relationship of any gene,
the genome as a whole, and the resulting phenotype.

4) For two important mutants, "diabetes" (db/db) and "obese,"
(ob/ob), the Bar Harbor Group (Dr. D. Coleman) provided excellent evi-
dence suggesting the central role of participation of the hypothalamic
satiety centre, which appears to be either abnormal in its response to
the normal stimulus for satiety (db/db), or else, although normal, fails
to respond as a result of non-production of the normal satiety stimulus
elsewhere in the body (ob/ob).

5) A most important additional conclusion, which may be already
drawn from work in Chinese hamster and mouse mutants as possible
"models" is, that the earliest gene-linked anomaly may affect

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intra-uterine, neonatal and/or immediate post-weaning feeding patterns, with or without dysfunction of the hypothalamus. Furthermore, these early and rather small changes in behavior must be and are capable of influencing the "clinical" characteristics of the diabetic syndrome developing days, weeks, or even months later. This was best seen, so far, with the Chinese hamster.

6) In the third of the three "models" which seem of special promise today, the spiny mouse (acomys cahirinus), it has been learned that the early insulin response to glucose is always and at all times delayed, even though normal rates of insulin secretion may be reached after prolonged glucose infusion. This pattern is similar to that observed in adult onset diabetics, and in at least some pre-diabetics, i.e. in those patients who conform to the definition of Cerasi and Luft. Accordingly, the spiny mice offer the quite unique opportunity to examine in minute detail, either morphological-ultrastructural (innervation, microtubulin system, membranes, etc.) or functional-biochemical (cyclic AMP system components, Ca^{++} movements, transmembrane potentials, etc.) properties that may be characteristically associated with the abnormal, delayed insulin release pattern, which is of such consuming interest to a great many human diabetologists.

7) Although nearly self-evident, it may be worth pointing out in closing that none of the conclusions listed in this very brief summary about small animals with short generation time (4 generations of mice per year, for example) would be accessible to study in man, since only "animal models" allow for precise testing and control of genetic factors, and also for precise testing and control of at least a reasonably large number of environmental factors. Genetic control, and/or true environmental control, cannot be managed in man, usually for legal reasons all the more convincing that ethical considerations would lead to the same conclusion. Were it possible to leave ethics apart, the constraints in time would still, for the present, result in the need for centuries, rather than for a few years, in order to obtain answers to essentially the same questions. However, once a "lead" or an answer has been obtained in an animal "model," it generally will be possible to devise one or several indirect means of testing for the applicability or non-applicability of that lead or answer in human diabetics or, perhaps more likely, in a specific group or a "type" of diabetic patient.

B. RECOMMENDATIONS FOR EARLY USE, THAT IS FOR APPROXIMATELY THE NEXT 18 MONTHS

1) With reference to paragraphs 3, 4, and 5 of section A., it is recommended as of immediate and urgent concern that there be no interruption in the programs designed:

(a) to detect all mutants occurring within the colony under observation for a good many decades as a result of the initiative of the founder of the Jackson Laboratories in Bar Harbor;

(b) to make available as widely as possible the mutants of interest to diabetes research; even though mutants once available in reasonable numbers, can and will be purchased by individual users, there is of necessity an initial period needed to define whether the mutant is of interest, whether it is a new mutation, whether the mutant is suitable for commercial distribution, all of which represents an investment for which funds should be made available upon recommendation by the Commission on Diabetes.

It is also recommended that the Jackson Laboratory scientists most interested in the metabolic mutants, especially Dr. Douglas Coleman, be asked whether the detection of mutants in this area could not be significantly accelerated and advanced if better biochemical screening of all animals in the colony were available. It is not always realized that up to this time mutants in the diabetes areas in the Jackson colony have only been detected when they also were obese -- since obesity can be seen, whereas hyperglycemia can not.

2) With reference to paragraphs 1, 2, and 5 of Section A., it is recommended that the Commission on Diabetes consider making funds available immediately to the Upjohn Company in order to increase (probably double) the size of the colony of Chinese hamsters and its sublines with a tendency to develop both non-ketotic and ketotic diabetes. The purpose of this immediate action would be principally that of increasing the availability of these valuable animals to all scientists and thus to encourage research projects with Chinese hamsters of defined genetic make-up. This in turn should hasten the definition of the role played by each of the four genes, two of which must be homozygous abnormal in order to produce hyperglycemia with ketoacidosis. Since doubling the colony would not suffice to cover the need for such animals in all interested laboratories, a recommendation on this point must also include the creation of a small committee of experts to be given the responsibility to attribute priorities to the projects for which the animals would be requested.

3) It is also recommended, with reference to paragraph 6, that steps be taken to ensure availability of spiny mice to those who wish to explore in depth the early phase of glucose-induced insulin secretion. This should be accomplished by increasing the size and productivity of the existing colony in Geneva, and also by encouraging the creation of several parallel colonies in Israel. The initial group of breeders for

some of the latter colonies should be obtained directly from the same area of the Neguev, where the ancestors of the Geneva colony were obtained, those for others should be taken from climatically similar areas but 100-300 miles distant from the first one.

4) Priority has so far been given in these recommendations to the three types of animal "models" presently considered most advanced and closest to at least partial "solution" as to the pathogenetic mechanisms concerned. It is, however, also and vigorously recommended that leads or possibilities of genetically isolating hyperglycemic syndromes in other animals, especially larger ones, should be pursued. Priority might be given to search for hyperglycemia, which will certainly be found, in the common laboratory rat, possibly beginning with (a) the most interesting, perhaps immunologically or virally induced accumulation of hyperglycemia and islet pathology in the animal breeding colony in Toronto. (b) So far, insufficient data has been published about Mystromys albicaudatus, the South African hamster, which is comparable in size to guinea-pigs. (c) A regular supply of sand-rats (Psammomys obesus) should be made available, preferably those originating from the Nile Delta in Egypt. Finally, even at this preliminary stage, it is recommended that a systematic search might be organized in zoos, since a number of occasionally hyperglycemic and ketotic rodents have been observed here and there, usually without a sufficient follow-up. Rodents come to mind first, but let us not forget the severely diabetic hippopotamus in the Tokyo zoo, or the poorly performing diabetic dolphins, in the San Diego Sequarium, which dramatically improved their performance when treated!

5) Emphasis in this part of the programme recommended to the Commission for Diabetes lays with spontaneous diabetes, as the possible revelator of mechanisms that may be operative, at least in part, in the pathogenesis of diabetes in man. Nevertheless, and even at this intermediary planning stage, there should be no discontinuation, indeed we recommend additional support and funding for studies with chronic experimental diabetes (surgical or chemical pancreatectomy), since neuropathy and retinopathy increasingly are being noted and can now be morphometrically quantitated in animals rendered diabetic for many months with streptozotocin, alloxan, etc. Coronary heart disease has been detected less frequently but the conditions of experimentation may not, so far, have been the best ones.

C. RECOMMENDATIONS FOR LONG-RANGE PLANNING (ONE TO FIVE YEARS AND BEYOND)

In order to prepare and coordinate as intelligently as possible developments after the next 12 or 18 months, this consultant

considers it mandatory to go through an intensive group discussion and reflection stage.

> [Just how important I consider this point is best illus-
> trated by a personal parenthesis, for which I apologize,
> but which I nevertheless believe should be included.
> It had been my own long-range project over the last few
> years, to make use of my appointment as Fogarty Inter-
> national Scholar for the purpose of organizing two
> planning periods at the NIH-Fogarty International Centre
> in Bethesda; the first two months were projected for
> summer or fall, 1975, with six to eight months, the
> main period, in 1976. I wanted first to plan, then
> bring together and stimulate, about three to six work-
> shops on spontaneous diabetes in animals dealing with
> several of the topics that I shall outline below as
> recommendations to the Commission. To my great chagrin,
> these plans had to be postponed because of my election
> by the Academic Senate of the University of Geneva to
> a five-year term as one of three Vice-Presidents of the
> University of Geneva. It would have been unthinkable
> for me not to accept since the change in plans was
> necessitated by the untimely death of my colleague and
> friend, who was then President of the University.
> Accordingly, to close this personal parenthesis, present
> plans would call for shifting the pre-consultation
> period of two months at the Fogarty Centre to the second
> half of 1976 or (if this long postponement should prove
> administratively possible at the Fogarty) with the
> actual workshops, planned in detail during the first
> 1976 stay, projected for May-December of 1978. So that
> you consider me as reasonably serious and organized,
> let me add that I shall then be entitled to a sabbati-
> cal leave of 15 to 18 months, from the fall of 1977 to
> the end of 1978.]

1) It is recommended that a panel, "of the hard-working variety," be appointed from the group of experts already familiar with either "models" considered "established" today, or promising new candidates; in addition to interest in the "models," the fields of expertise of the panelists should include genetics, virology, immunology, ultrastructure, data processing and storage. Although it is essential that the early period of activity of the panel should allow for expression of as many points of view as possible, it is nevertheless also recommended that the total membership of this main panel should not exceed 25 persons. The concept does, of course, call for much work being prepared or later carried out through much smaller subcommittees.

2) <u>The mandate given to the panel should be the following:</u>

    (a) to define the best conditions for <u>safekeeping and adequate production</u> of "models" already available;

    (b) to work out the <u>mechanisms for the allocation</u> of animals according to wide open competition, priority being given to the qualitatively best research projects proposed, also taking into account that a wide range of questions of different nature needs to be pursued;

    (c) to select the <u>best mechanism for "storage"</u> of all new mutants which <u>might</u> be of interest, in order to preserve potentially valuable mutations for later study. For example, a very low temperature storage facility for embryos, resembling that already existing for cell lines, was suggested by Dr. Coleman at the meeting;

    (d) <u>to review at intervals the information available on each "model,"</u> as well as the relative priority of each "model" against the others, priority which might result from the overall results available at that time, leading also to priority (or not) for the scarce production facilities.

    (e) to propose an <u>information-storage system concerning each "model,"</u> since it would seem likely that many advances will result from the <u>comparison of different models</u>, and that such comparative information might prove more revealing than the straight description of just one model, or just a very few "models";

    (f) to propose the <u>best mechanism to ensure a rapid flow of information</u>, presumably through one or more annual working meetings, since the written word is and remains slower than personal contacts and the spoken word;

    (g) <u>to work towards international composition of the panel</u> and the gathering of information through collaboration with other scientific support bodies and diabetes-related association in foreign countries.

3) It is also recommended that a second panel, very similar to the first as to its mandate, be created in order to facilitate the flow of information, and to provide optimal conditions for the most wide-spread utilization of the exceptional investment represented by animals with chronic experimental diabetic syndromes, often of one to ten years' duration, usually kept and investigated for the occurrence and genesis

of complications such as microangiopathy generally, retinopathy, nephro-
pathy, disturbed function of the central and the peripheral and autonomic
nervous systems, cardiovascular complications related to coronary artery
disease, etc.

4) <u>Timetable</u>: It would seem reasonable to expect that specific and
quite complete <u>recommendations might be worked out by the panels during
the calendar year 1976</u>, and practical implementation would be gradually
effected through 1977, 1978, and beyond.

Editor's note: for further information the reader is referred to
Renold, Albert E., Spontaneous and Experimental Diabetic Syndromes in
Animals. A Re-evaluation of their Usefulness for Approaching the
Physiopathology of Diabetes. In: Malaisse, W. J. and Pirart, J.,
Diabetes: Proceedings of the Eighth International Diabetes Federation,
Brussels, July 1973. Excerpta Medica, Amsterdam.

GENETICS OF DIABETES MELLITUS

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Hereditary factors are generally accepted to be of great importance in the etiology of diabetes, but there is little agreement as to the nature of the genetic mechanisms involved (Rimoin, 1971; Rimoin and Schimke, 1971; Simpson, 1971). Evidence in favor of a large genetic component in the etiology of diabetes is based primarily on studies of the familial aggregation of the disease, twin studies and population studies using markers such as clinical diabetes, glucose tolerance testing, insulin secretion and basement membrane thickening (Burkeholder et al., 1967; Cerasi and Luft, 1967; Conn and Fajans, 1961; Gottlieb and Root, 1968; Harvald and Hauge, 1963; Neel, 1970; Pincus and White, 1933; Pyke and Taylor, 1967; Rimoin and Schimke, 1971; Simpson, 1964). Regardless of the marker used, be it clinical diabetes or abnormal glucose tolerance, there is a significantly greater prevalence of abnormality among the relatives of diabetics than among similar relatives of nondiabetics. In almost none of these studies, however, were individual family units examined, nor was there any attempt to define different genetic forms of diabetes. Although the evidence derived from studies of familial aggregation and twins leaves no doubt as to the importance of genetic factors in the etiology of diabetes, the mode of inheritance of the diabetic trait(s) is unknown (Rimoin, 1971; Rimoin and Schimke, 1971). During the past several decades, every possible mode of genetic transmission has been proposed, objections to all of them have been raised, and yet even today there are proponents of each of these hypotheses. This disagreement is due in part to a number of obstacles to which the geneticist is confronted in his attempts to unravel this problem. These include vast differences in the definition; in some an affected individual must have significant clinical symptoms of the disease, while in others only a mildly abnormal glucose tolerance test is accepted. The clinical variability, variability in the age of onset of the disease, and susceptibility to environmental factors present further difficulties in the delineation of an affected individual. Furthermore, the high prevalence of the disease in the population raises questions of relative genetic fitness. The most important impediment to genetic analysis, however, is the lack of knowledge concerning the basic defect in diabetes. Because of this, there is no certain method for detecting prediabetics, i.e., individuals with the mutant genotype who have, as yet, no signs of carbohydrate intolerance.

Although the mode of transmission of the diabetic genotype is obviously in question, many investigators have accepted the autosomal recessive hypothesis as fact and have based their definition of 'prediabetics' on this assumption. If such were the case, all offspring of two diabetics must possess the diabetic genotype. However, only about 50% of such individuals have been found to be affected, irrespective of the marker used to define diabetes (Kahn et al., 1969; Navarrete and Torres, 1967; Siperstein et al., 1968; Taton et al., 1964). These observations may be the result of several factors, including lack of penetrance, since accurate markers of the diabetic genotype are not available. Secondly, these data would be expected if diabetes was not inherited as a simple, autosomal recessive trait, but as a dominant or polygenic trait. Multiple factors are certainly involved in the variability of normal blood sugar levels but polygenic inheritance as a cause of clinical diabetes mellitus has not been adequately proven. Indeed, recent studies by Steinberg et al. (1970) have demonstrated bimodality in blood sugar concentrations in populations with a high prevalence of the disease. Thirdly, diabetes mellitus may be a heterogeneous group of disorders, i.e., a number of distinct disorders caused by different gene mutations at different loci, each of which results in carbohydrate intolerance (Rimoin, 1971; Rimoin and Schimke, 1971).

Evidence in favor of the heterogeneity hypothesis includes (a) clinical variability in the disease, as exemplified by the differences between juvenile onset and maturity onset diabetes; (b) genetic variability, as exemplified by the dominantly inherited forms of maturity onset type of diabetes in the young, the other nondominant forms of genetic diabetes and the newly described forms of nongenetic diabetes in juvenile onset forms; (c) ethnic variability in the clinical and metabolic features of diabetes apparently not directly related to environmental factors; (d) syndromes associated with glucose intolerance -- there are well over 30 distinct genetic syndromes due to mutations at different loci as well as several chromosomal aberrations (Table 1); (e) biochemical heterogeneity in the disorder -- e.g., variability in insulin and glucagon responses in different diabetics (see Fajans remarks); (f) immunological variability in the disorder -- see Nerup's talk for evidence of diabetic syndromes associated with islet specific antibodies; (g) twin studies -- see Pyke's studies for definite heterogeneity in juvenile monozygotic twins; and (h) differences in HLA types in different forms of diabetes -- (see Nerup's talk). Furthermore, genetic heterogeneity has been well documented in the mouse, being associated with at least four simply inherited disorders due to mutations at different loci as well as being present at high frequency in a number of different strains which have been developed by selection and inbreeding (see Coleman's talk). Thus, all of this evidence points toward the possibility that diabetes

TABLE 1

<u>GENETIC SYNDROMES ASSOCIATED WITH GLUCOSE INTOLERANCE</u>

<u>SYNDROMES ASSOCIATED WITH PANCREATIC DEGENERATION</u>

 Hereditary Relapsing Pancreatitis
 Cystic Fibrosis
 Polyendocrine Deficiency Disease
 Hemochromatosis

<u>HEREDITARY ENDOCRINE DISORDERS WITH GLUCOSE INTOLERANCE</u>

 Isolated Growth Hormone Deficiency
 Hereditary Panhypopituitary Dwarfism
 Laron Dwarfism
 Pheochronocytoma
 Multiple Endocrine Adenomatosis

<u>INBORN ERRORS OF METABOLISM WITH GLUCOSE INTOLERANCE</u>

 Glycogen Storage Disease Type I
 Acute Intermittent Porphyria
 Hyperlipidemias

<u>SYNDROMES WITH NON-KETOTIC INSULIN RESISTANT EARLY ONSET DIABETES</u>

 Ataxia Telangiectasia
 Myotonic Dystrophy
 Lipatrophic Diabetes Syndromes

<u>HEREDITARY NEUROMUSCULAR DISORDERS WITH GLUCOSE INTOLERANCE</u>

 Muscular Dystrophies
 Late Onset Proximal Myopathy
 Huntington's Chorea
 Machado Disease
 Herrmann Syndrome
 Optic Atrophy - Diabetes Mellitus Syndrome
 Friederich's Ataxia
 Alstrom Syndrome
 Laurence-Moon-Biedl Syndrome
 Pseudo-Refsum Syndrome

TABLE 1 (Continued)

PROGEROID SYNDROMES WITH GLUCOSE INTOLERANCE

    Cockayne Syndrome
    Werner Syndrome

SYNDROMES WITH GLUCOSE INTOLERANCE SECONDARY TO OBESITY

    Prader-Willi Syndrome
    Achondroplasia

MISCELLANEOUS SYNDROMES WITH GLUCOSE INTOLERANCE

    Steroid Induced Ocular Hypertension
    Mendenhall Syndrome
    Epiphyseal Dysplasia and Infantile-Onset Diabetes
    Stimmler Syndrome

CYTOGENETIC DISORDERS WITH GLUCOSE INTOLERANCE

    Trisomy 21
    Klinefelter Syndrome
    Turner Syndrome

represents a heterogeneous group of disorders and that hyperglycemia is a nonspecific manifestation of a variety of different mechanisms. Indeed, hyperglycemia may be no more specific than anemia and the use of insulin may be as nonspecific as a blood transfusion.

Theoretically, there are a number of ways in which a gene mutation could affect insulin synthesis, secretion, transport, or action so as to produce carbohydrate intolerance. Some of these possibilities include a structural mutation in the insulin molecule, a defect in the enzyme which cleaves insulin from proinsulin, decreased synthesis or secretion of a normal insulin molecule, glandular hypoplasia or degeneration, peripheral unresponsiveness to the actions of insulin, or circulating antagonists to insulin action. It is likely that many, if not all, of these mechanisms do produce abnormal glucose tolerance, and future research into this symptom-complex must provide a means of identifying the specific pathogenetic mechanism operative in each diabetic patient before accurate genetic counseling can be given.

Since the mode of inheritance of diabetes is still in question, accurate genetic counseling is impossible. Various tables listing the risk of an individual inheriting the diabetic genotype have been published, based on the assumption that diabetes is inherited as a simple autosomal recessive trait (Grunnet, 1957) or on the basis of a statistical analysis of morbid risk figures, calculated from a limited clinical experience (Simpson, 1968). Simpson (1968, 1971) has constructed relative risk figures for developing clinical diabetes among first degree relatives of diabetics, based on data obtained from questionnaires on a large population (Table 2). The risk of a given relative developing diabetes varies with the age of onset of diabetes in the proband. If the proband developed diabetes under the age of 20 years, the risk figures should

TABLE 2

RISK OF DEVELOPING DIABETES WITH A PARENT, SIBLING
OR CHILD WHO IS A DIABETIC (SIMPSON, 1971)

Age of nondiabetic (years)	Risk of developing diabetes
0–19	>1%
20–39	1%
40–59	3%
60+	10%

be approximately doubled, except for the over 60-year-old category. If there is more than one parent, sibling or child who is diabetic, the risks are also approximately doubled. These relative risk figures are, of course, approximations and must be related to the age-specific risk for

diabetes in the specific population from which the counselee is derived. Although these risk figures allow one the satisfaction of quoting a number to the counselee, he should be made aware of its inexactness.

There has recently been some controversy on whether or not diabetics should be allowed to marry one another and have children. The World Health Organization (1965) advises that diabetics should be counseled not to marry each other, or if they do, they should not have children. They base this advice on the presumption that 'conjugal diabetics may increase the number of diabetic offspring and perhaps determine the appearance of diabetics at earlier ages.' Edwards (1969) has pointed out the fallacy of this advice and claimed that these recommendations would probably not increase the number of subsequent diabetics, but simply influence their allocation. It is apparent that with our limited knowledge concerning the genetics of diabetes, it is difficult to offer informative genetic counseling to an individual couple, and foolhardy to attempt eugenic measures.

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RECOMMENDATIONS FOR FUTURE STUDIES IN THE GENETICS OF DIABETES

David L. Rimoin, M. D. , Ph.D.

1. Extensive family studies of diabetes mellitus. Study complete family units of diabetic and control probands in terms of all known parameters of carbohydrate metabolism; e.g. clinical features of the disease, insulin glucagon and growth hormone responses, basement membrane thickening, HLA and LD types, viral titers, etc. Look for variability in these parameters which may define different forms of diabetes mellitus and study to see whether they might breed true within families. Study the variability of the parameters in concordant monozygotic twins to determine the possible variability of glucose intolerance caused by a single gene mutation, evaluate the offspring of two diabetic parents separating these families into those types in which the parents have similar or different forms of diabetes. Each of these studies should be done by performing segregation analysis within individual families followed by grouping of clinically and biochemically homogeneous forms of diabetes for larger sample analysis.

2. Extend the studies into the genetic syndromes associated with diabetes mellitus in an attempt to define all possible mechanisms by which a gene mutation can result in glucose intolerance. Examine these parameters in the heterozygous carriers of such mutant genes in an attempt to define specific loci which can lead to a predisposition to glucose intolerance.

3. Extend the studies of Pyke and Nerup to define clinical and metabolic differences between acquired and genetic forms of diabetes.

4. Define the clinical and metabolic features of glucose intolerance in different ethnic groups in an attempt to define the specific types of diabetes present in different populations and set standards for normal glucose tolerance in each of these populations.

Since the majority of these studies involve rare mating types, rare genetic diseases or unusual twin pairs, the most likely way of achieving these goals would be to develop a large collaborative study in which a number of different investigators throughout the country performed similar studies under a defined protocol. These might utilize central laboratory services as well. Such a collaborative study would allow valid samples to be accumulated to test each of the above questions.

THE ASSOCIATION OF DIABETES MELLITUS AND OBESITY

George A. Bray, M.D.

A. The Association of Diabetes Mellitus and Obesity

1. Clinical Studies

The early studies of Joslin, Dublin, and Marks in 1935 (1) demonstrated an important relationship between obesity and diabetes mellitus. They noted that a third or more of the diabetics were more than 20% overweight and that more than 60% of these patients were above their desirable weight as defined by life insurance statistics. These pioneering observations have been confirmed and extended by a number of more recent studies. Pyke and Please (2) examined the relationship between diabetes and obesity in 946 outpatients and noted that the frequency of obesity was lowest in the diabetics under age 30 and highest in diabetics between 30 and 60. In those over 60 years of age, the frequency of obesity was intermediate between those of the youngest and middle-aged group. This distinction between juvenile and adult onset diabetes based on the body weight has also been observed by Keen who compared the development of diabetes among civil servants in London in relation to body weight (3). Those who were overweight developed diabetes more frequently than those with a stable body mass index. Family statistics also support this concept. Using the first member of a family with diabetes as the index case (propositus), Baird has examined the prevalence of diabetes in lean and obese siblings (3) (Table 1). Among the obese siblings of diabetics, the frequency of diabetes was higher than in the lean. This suggests that the obesity had placed an extra burden on the pancreas of these diabetics which may have precipitated clinical disease. One estimate of the relationship between diabetes and obesity was published by Rimm et al. (4) in an investigation of 73,000 respondents to a questionnaire to members of the TOPS Clubs (Take Off Pounds Sensibly). Increasing body weight and age were both associated with the rising frequency of diabetes mellitus (Fig. 1). Less than 1% of normal weight women aged 25 to 44 had diabetes mellitus whereas 7% of those of the same age who were 100% overweight had this complication. Weight gain after age 20 may play a particularly important role in the development of diabetes mellitus. This concept has been examined by comparing the percentage increase in body weight for males and females between age 25 and 65 in four countries with the mortality from diabetes (Table 2). The mortality from diabetes mellitus was highest among those who showed the greatest weight gain between age 25 and 60. Women living in Canada and the United States showed the greatest percentage increase in body weight and had the highest mortality from diabetes. Japanese women, on the other hand, had a very small weight gain between age 25 and 60,

and showed a very low incidence of body weight. Finally, West and Kalbfleish (5) related the incidence of diabetes in obesity and the degree of overweight in several countries. As the relative weight increased from country to country, the frequency of diabetes also increased. However, not all obese patients developed diabetes.

2. Experimental Studies

Several species of experimental animals have both diabetes and obesity (6,7). In some of these, the abnormality is genetically transmitted and in others it is primarily the result of environmental changes. The Wellesley mouse and the desert sand rat (Psammommys obesus) are examples of the latter group. The Wellesley mouse (C$_3$HfI) and the sand rat developed obesity and diabetes when allowed to eat laboratory food ad libitum. Restriction of dietary intake will prevent the development of diabetes mellitus and obesity. Among animals with genetically inherited forms of obesity, prevention of weight gain may reduce blood sugar, but it does not prevent the appearance of most of the manifestations of this syndrome. However, in the animals allowed to eat ad libitum, the severity of the hyper-glycemia becomes considerably worse. Experimental evidence suggests that obesity increases the demand on the pancreas to produce insulin. When the pancreas is unable to meet these demands because it has been injured by chemical, viral or genetic factors, the demands of obesity cannot be met and this may lead to failure of the pancreas. An entirely normal pancreas, however, can apparently meet the demands of extra insulin production imposed by obesity.

From these clinical and laboratory areas of investigation, it is clear that obesity is an important precipitating factor in the develop-ment of diabetes mellitus. Understanding of the mechanisms underlying the development of diabetes in the obese animal and man might provide tools for dealing with this problem.

B. Status Reports in This Area

A number of books and monographs have reviewed the relationship of obesity to diabetes and the current state of knowledge about obesity. These are listed below:

1. Obesity in Perspective. Fogarty International Center Series on Preventive Medicine, Vol. II, Part 1 and Part 2 (G. A. Bray, Ed.) U.S. Gov't Printing Office, Washington, D.C. (in press) 1975

2. Bray, G. A. and J. E. Bethune (Editors). Treatment and Management of Obesity. Harper & Row, Hagerstown, Md. 1974

3. Garrow, J. S. Energy Balance and Obesity in Man. North-Holland; Amsterdam, The Netherlands, 1974

4. Craddock, D. Obesity and Its Management. The Williams and Wilkins Co., Baltimore, Md. E & S Livingstone, Ltd. Edinburgh and London 1969

5. Obesity Symposium, December 4th/5th, 1973. Servier Research Institute (W. L. Burland, J. Yudkin and P. Samuel, Editors), London, 1974

6. Asher, W. L. Treating the Obese, Medcom Press, 1974

7. Lasagna, L. (Editor) Obesity Causes, Consequences and Treatment. Medcom Press, 1974

C. Recommendations for Treatment

The abnormal glucose tolerance tests and high insulin requirements of obese patients can, in some instances, be reversed by weight loss. This would ameliorate diabetes mellitus. Thus, effective approaches to treating obesity would be expected to significantly reduce the problem of diabetes mellitus. Toward this goal of reducing the ravages of diabetes in the obese patient, additional studies are needed on:

a. The mechanisms by which the body recognizes its caloric stores and regulates food intake under a variety of experimental conditions.

b. The techniques by which we can identify those individuals predisposed to develop obesity.

c. The effectiveness of various therapeutic methods for the treatment of obesity.

Specifically, dietary factors seem to be important in the development of obesity and in development of diabetes mellitus, atherosclerosis and hypertension as well. Because of this important interrelationship, a national committee should be formed to carefully review the role of daily diet in American life. Governmental commissions in England (8) and Sweden (9) have undertaken such a review; similar action on the part of the American government would appear to be warranted. A reduction in the quantity of fat in the diet, decrease in total calories, and an increase in the amount of exercise would be expected to have important health benefits to the nation.

D. Recommendations for Research

      a. The relationship between experimental diabetes and the development of obesity in animals requires additional definition particularly in the genetically transmitted forms of obesity.

      b. Studies on the interaction of dietary factors and the tendency to develop obesity and diabetes mellitus is also necessary as a rational basis for dietary prescription.

      c. Further studies on the role of sucrose and the development of obesity, glucose tolerance and diabetes would be of value since sucrose has been implicated in the precipitation of diabetes in animals.

TABLE 1.

Weight Status of Diabetic Propositus	Frequency of Diabetes among siblings in two weight groups	
	Obese	Nonobese
	%	
Obese	10.8	4.8
Nonobese	27.3	7.3

Adapted from Keen (1975).

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TABLE 2.

Country	Increase in Weight between 25 and 60 yrs.		Mortality from Diabetes[o]			
			Over 45		All ages	
	M	F	M	F	M	F
		%				
Japan	0.4	0.4	–	–	2.4	2.0
England	3.6	15.5	14.0	25.2	5.3	10.1
Canada	4.6	19.3	55.6	91.5	16.2	24.5
United States	8.1	15.0	67.7	111.6	20.7	34.0

[o] Mortality rates per 100,000 population in 1948

After Hundley (1956)

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RELATIONSHIP OF OBESITY AND DIABETES MELLITUS

Philip Felig, M.D.

A relationship between obesity and diabetes has long been recognized. Sixty to eighty per cent of adult-onset diabetics are obese. Furthermore, obesity is associated with increased insulin secretion as well as insulin resistance. The latter is demonstrable in each of the target tissues of insulin action, notably, the liver, muscle tissue and fat cell. Despite a marked increase in our understanding of insulin physiology in obesity, major questions remain. Specifically, it is unclear whether increased insulin secretion procedes or follows the development of insulin resistance. If insulin resistance is the primary factor, the nature of the signal to the beta cell eliciting augmented insulin secretion remains to be established. On the other hand, if increased insulin secretion antecedes insulin resistance, the mechanism whereby the latter is brought about also requires elucidation. In addition, the relative importance of such factors as hyperphagia and the composition of the diet in the development of the hyperinsulinemia -- insulin resistance of obesity is still unclear.

The importance of pursuing studies with regard to insulin physiology in obesity relates to two major considerations. (1) Obesity represents quantitatively the most important, potentially reversible factor influencing the development of the diabetic state. Although hereditary factors and possibly acquired factors other than obesity (such as viral infections or autoimmune changes) contribute to the pathogenesis of diabetes, at the present time none of these factors other than obesity is potentially alterable. (2) Reduction in body weight to or toward normal results in amelioration of the diabetic state in most obese patients. In view of the latter it is clear that development of successful management programs for the treatment of obesity would have a major impact in improving the health of adult-onset diabetes. The need for research on dietary management of obesity is underscored by the dismal record of virtually all dietary programs attempted in the past.

In summary, obesity represents the most important, potentially reversible or preventable factor contributing to the development of diabetes. Research is clearly needed (1) to increase our understanding of insulin secretion and insulin resistance in obesity; and (2) to develop more effective therapeutic modalities than those currently available.

OBESITY AND DIABETES MELLITUS

Jules Hirsch, M.D.

If one can accept the premise that all metabolic states characterized by a diminished capacity for the utilization of glucose are a form of diabetes or at least a diabetic-like state, then obesity could be considered the most prevalent form of diabetes in the United States. Depending on definitions, nearly one-third of the American public is obese; furthermore, it is becoming increasingly clear that the obese individual behaves, in a metabolic sense, as though they have a scarcity of glucose and an inability to correctly perceive the abundant glucose that is ingested and present in body fluids.

Thus:

1. Peripheral tissues utilize relatively more fatty acid as energy substrate as though to conserve glucose supplies in the obese.

2. There is an hepatic over-production of glucose.

3. Hyperphagia and under-activity almost always in evidence, lead to the acquisition and conservation of more glucose and calories.

In the presence of obesity, diabetes occurs with greater frequency and is more difficult to treat. Thus, in a clinical sense, the very close relationship between these two disorders can be seen. Furthermore, in the mild, maturity-onset diabetic, treatment of moderate obesity is often the first line of defense against worsening of the diabetic state.

Current efforts to effect permanent weight reduction in the obese are at best only partly successful. This stems in large measure from a lack of adequate understanding as to the metabolic role played by the obese state and what appears to be the "essential" nature of compensating for metabolic features still poorly understood. A life long conditioning to overeating and under-activity may bring this situation about or there may be basic genetic factors involved which could be conditioned by nutritional practices.

In any event, it would seem essential that:

1. A deep understanding of the metabolic determinants of obesity become a major aspect of research in diabetes.

2.   A closer liaison be developed between current obesity and diabetic research facilities.

3.   Greatly expanded research efforts in the basic mechanisms of fat storage and caloric intake be undertaken.

RECOMMENDATIONS ON OBESITY

Ethan A. H. Sims, M.D.

I. The Need for Coordination of Work in Obesity and Diabetes.

Since adult-onset, non-insulin-dependent diabetes is the commonest form, since obesity is associated with insulin resistance, and since at least 70 per cent of such diabetic patients are obese, it appears logical to provide centers in which research, education, and service for obesity and for diabetes are combined or at least are very closely coordinated. Extending this one step further, since both diabetes and obesity are recognized risk factors for cardiovascular disease, investigative and therapeutic efforts for the three problems, as well as rehabilitative programs should be closely coordinated or shared. To date there has been compartmentation of effort which has been wasteful of talent and facilities. The National Commission could provide opportunities for bridging or uniting these areas of common interest.

II. The Need for Adequate Classification of Obesity and Contributory Factors.

Obesity has usually been considered as a single entity ("exogenous" obesity) and this has confounded the results of research studies and frustrated attempts to evaluate therapeutic efforts. It is possible now at least to classify obesity into one or other of two groups: the hyperplastic-hypertrophic, with increase in fat cell number and usually early onset, and the hypertrophic of later onset. A further etiologic or anatomic description can often be made, together with family history relevant to obesity and diabetes and an evaluation of contributory factors. (See Vol. I of the Fogarty Center Report on Obesity for a provisional clinical classification.) I suggest that the National Diabetes Commission take the initiative in standardizing a system of classification and a data base both for obesity and for diabetes. Standards for estimating the degree of obesity should also be defined.

III. Some Needs for Further Research.

1) The genetic role of obesity is well established in animals, but more studies, such as those of children adopted at an early age or of twins, which are designed to differentiate the effects of environment vs heredity in the various types of obesity are needed.

Recognition of a genetic factor in a given case may do much to alleviate the tendency to blame the patient on the part of the family, peers, and physicians and to alleviate guilt on the part of the patient.

2) Controlled, preferably randomized prospective studies of the effects of early nutrition, such as breast vs. bottle feeding, on subsequent development of obesity are needed.

3) Marked individual differences in efficiency of weight gain from excess calories and also differences in the response to diets of varying composition have been demonstrated recently. More definitive, long-term studies in this area are needed, and this in turn requires more adequate support of staff who can devote full time to such studies and more adequate provision of clinical study unit facilities. Specialized and costly facilities, such as environmental chambers, are available in a number of institutions, but the need is for people qualified to devote full time to their operation.

4) To date controlled prospective studies of the relative effects of various treatment regimens, such as the UGDP study, have included only relatively minor efforts to affect the course of the metabolic disorder by diet alone, and none by diet plus exercise and physical rehabilitation. The UGDP study has led to the recommendation that if diet (as conventionally applied) fails, insulin should be used, but this is illogical in obese diabetics who have insulin resistance secondary to their obesity and overfeeding, and who still have a reserve of beta cell function. There is at least preliminary evidence that intensive weight reduction and physical conditioning may reverse the clinical diabetic state, at least when the pancreatic reserve has not reached a point of no return. Definitive, controlled, prospective studies to evaluate the effect of such measures are critically needed. To facilitate studies involving prescription of exercise, improved means of prescribing and also of monitoring activity as a treatment variable should be developed.

5) The long-term success rate in treatment of early onset obesity of the hypercellular type with early onset is meager. Many such patients are now treated by intestinal bipass, which carries a high risk:benefit ratio. It remains to be established whether the regimen of protein-sparing partial starvation introduced by Apfelbaum and promoted by Blackburn has a place in any stage of their treatment. Behavioral modification is an approach which gives promise of enabling patients to sustain weight loss and should be evaluated in this refractory group of patients. This will require longer followup than the usual period of six months or a year. For purposes of followup studies in particular, a registry of patients with serious obesity, similar to the Tumor Registry now in operation, would be useful.

IV. Some Needs for Education and Community Service.

A Saturday morning watching TV will show that this country is engaged in an educational campaign, commercially sponsored, which is calculated to promote later development of obesity and diabetes in the young people to whom it is directed. Emphasis is placed on junk foods high in carbohydrates and on the easy way of doing things, preferably with the aid of the internal combustion engine. For adult viewers exaggerated or misleading claims are made for weight reduction regimens, and often the seriously obese person is ridiculed in cartoons or advertisements. There is need first of all for the medical profession and nutritionists to agree upon what form of diet is appropriate for which type of obesity or diabetes, for the public is confused, and then to educate patients as to the risk factors and the options for treatment. This could be accomplished partly through parents, schools, and physicians, but it will be necessary also to influence what is presented via the news media and TV and to take an active part in education through these channels.

It is apparent that obesity is increasing in this and other affluent countries and along with it non-insulin dependent diabetes. Early in our evolution we acquired the equipment to store fat efficiently and to survive prolonged fasting, but in our present society in which physical inactivity is promoted and in which there is continual pressure of food supplied in excess, the capability for storing fat is a liability. Rather than treating degenerative complications when they occur, what is needed is a change in life style, particularly in those families where there is a strong inherited tendency toward obesity and diabetes. It might be possible to obtain more lasting educational effects and to reach younger people more effectively if high-risk families could be treated as a group in centers at which a family could board for several weeks while their patterns of activity and eating were analyzed and efforts made to initiate acceptable alternative patterns of living. Could the National Commission recommend support of several centers for a pilot study along these lines?

Finally, there are changes which are required if people in our larger cities are to be more physically active. Safe pathways for walking, cycling, or jogging are needed. Similarly, just as by law it is required that exits be clearly marked, stairways, as an alternative to elevators, should be identified, and in new construction should be placed near the elevators.

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NUTRITIONAL CONSIDERATIONS IN DIABETES MELLITUS

Theodore B. Van Itallie, M.D.

Of the many nutritional considerations that are relevant to the problem of diabetes mellitus, obesity appears to be the most important. The association between obesity and maturity-onset diabetes is well recognized, but the nature of the relationship between the two conditions remains poorly understood. For example, it is not yet clear whether obesity and maturity-onset diabetes are both manifestations of the same underlying disorder, or whether obesity is merely a "stress factor" that precipitates chemical or clinically manifest diabetes in susceptible individuals.

If the etiologies of obesity and diabetes are intertwined, then research into the cause or causes of obesity may also throw light on the pathogenesis of adult-onset diabetes. But, apart from study of pathogenetic mechanisms, the development of more effective methods for the control and treatment of obesity is clearly of critical importance in the control and treatment of adult-onset diabetes mellitus. Thus, investigation oriented toward obesity prevention and treatment should engage the attention and support of agencies concerned with the funding of diabetes research.

As regards the etiology of obesity, the issues might be summarized in terms of questions such as the following:

1) What proportion of obesity is genetically determined?

   a) Is "genetic" obesity a function of hyperplasia (with subsequent hypertrophy) of adipose cells or does it result from a central "ponderostat" that is set "too high?"

   b) Do some obese individuals suffer from a subtle defect of thermogenesis? Are they therefore unable to respond to an excess load of calories by increasing heat loss to the same extent as lean individuals?

   c) Do obese individuals have some inherent defect in their satiety mechanisms such that increasing energy stores do not act to inhibit appropriately the rate of caloric ingestion?

2) Can obesity in adult life be ordained by overeating during certain critical periods during childhood?

a) Does overeating during childhood induce sufficient hyperplasia of adipocytes to create a form of constitutional obesity that tends to persist during life?

3) To what extent is obesity, particularly the moderate obesity of middle life, a product of simple physical inactivity and therefore remediable by an appropriate increase in physical activity?

4) To what extent does obesity result from the non-nutritive "abuse" of food?

a) Do many people overeat at times because they are using the eating process inappropriately to solve non-nutritional problems (e.g., boredom, unhappiness, etc.)?

b) Are some individuals more susceptible to food related cues in the environment and therefore "at risk" in a setting where a variety of palatable food products are readily available?

Of the above questions, the ones related to genetic considerations are perhaps most relevant to the problem of adult-onset diabetes mellitus. For example, there is evidence that insulin-sensitive "glucoreceptors" in the hypothalamus and elsewhere may play a role in the regulation of food intake as well as in glucose homeostasis. Clearly, a subtle change in the metabolic behavior of such specialized neurons might affect both energy balance and glucose homeostasis.

Ideally, prevention and treatment of obesity should be grounded in knowledge about pathogenesis. But until more is known about etiology, prevention and treatment must proceed on an empirical basis or "as if" etiology were understood. Thus, we now attempt to prevent some forms of obesity by directing clinical attention to potentially obese infants and children who appear to be a risk for a variety of reasons. Behavior modification therapy is likely to be most effective in situations where food is used for non-nutritive purposes. If some patients have elevated ponderostats, appropriate pharmacological treatment may be the best ultimate answer.

Despite the obvious importance of obesity in relation to diabetes, there has been insufficient emphasis by NIH (and other agencies concerned with these problems) on the need to encourage much greater collaboration between investigators and groups conducting research in diabetes and those conducting research in obesity. Where possible, obesity research centers and diabetes research centers should be set up in juxtaposition and they should be required to function in a complementary fashion. More workshops should be designed to bring together key investigators concerned with certain aspects of diabetes research and those concerned with obesity research. Finally, those who

fund diabetes research should recognize the practical importance of supporting programs that offer promise in advancing knowledge of both the causes of obesity and its treatment.

Although obesity is a key issue in diabetes research, other nutritional considerations pertinent to diabetes should not be neglected. Of enormous importance is the disposition of the diabetic patient prematurely to develop clinical manifestations of athero-sclerosis, particularly coronary heart disease and peripheral vascular disease. Diabetic arteries, perhaps because of associated small vessel disease, seem more susceptible to atheromatous degeneration; accordingly, in diabetic patients it may be particularly important to attempt to maintain low-density and very low density lipoproteins in the plasma at the lowest feasible concentrations. Reduction of serum lipids can be accomplished by an appropriate diet in most instances. A key subject for research continues to be diabetic vascular disease (including small and large vessels) and, in particular, the apparent susceptibility of the diabetic artery to artheromatous transformation.

Recently, evidence derived from in vitro studies has accumulated indicating that the platelets of patients with diabetes mellitus (even with those with "chemical" diabetes) may have an enhanced disposition to aggregate and may exhibit increased "stickiness." If such in vitro changes denote a genuine thrombogenic diathesis, this fact could account in part for the increased incidence of early myocardial infarctions in diabetic individuals. This matter is relevant to nutrition because it has been shown that diets rich in linoleic acid content can reduce platelet aggregatability. The mechanism may involve an increased rate of production of prostaglandin E_1 (PGE_1) vis-à-vis PGE_2.

As for other dietary factors, the nutritional research reported to date does not appear to have uncovered any clues of major importance bearing on the problem of diabetes mellitus. A possible exception is the work relating chromium nutriture to impaired glucose tolerance in laboratory animals and, perhaps, some human subjects. However, the impaired glucose tolerance that accompanies chromium deficiency probably is not relevant to the pathogenesis of either growth-onset or adult-onset diabetes. It appears that the relatively few patients who "benefit" from chromium supplementation are elderly persons without overt diabetes but with mildly to moderately impaired glucose tolerance. It is not clear that acceleration of the glucose disposal rate in such patients serves any useful clinical purpose.

SUMMARY OF PRESENTATION TO WORKGROUP MEETING OF THE
NATIONAL COMMISSION ON DIABETES, COMMITTEE ON
ETIOLOGY AND PATHOLOGY

Peter James Dyck, M.D.

There appear to be several types of peripheral neuropathy associated with diabetes millitus:

Mononeuropathy - Cr. III and others

Mixed Distal - pseudotabes
              - Hyperalgesic
              - autonomic

Lumbosacral radiculoneuropathy

Neuropathy associated with peripheral vascular disease

The pathogenetic mechanism of the development of the last is well known, but much uncertainty exists regarding the others. Historically major views held for the mechanism producing neuropathy include large vessel ischemia, small vessel ischemia, metabolic derangement of nerve cells and Schwann cells resulting in a parenchymatous degeneration of the distal aspect of nerve cells, or in segmental demyelination from Schwann cell disease. By application of three-demensional studies of the pathology of the peripheral nervous system in man with diabetes millitus, it should be possible to arrive at a tentative conclusion as to whether the peripheral neuropathy of diabetes is likely to be from vessel ischemia, inflammation -?immunologic cause, or is a parenchymatous degeneration of nerve cells or of Schwann cells. Studies such as the ones that I am proposing would include morphometric analysis of various levels of fasciculus gracilis, of various spinal roots, of spinal ganglia, of plexus and of various levels of peripheral nerves. Such studies have in the past been very helpful in understanding the nature of the fiber degeneration as related to the region of vascular occlusion in vasculitis and inflammotory neuropathy. A variety of studies using psysiological, pharmacological, biochemical, immunological and other disciplines are needed. One can think of a variety of studies that could be done almost immediately in human diabetes millitus. Eventually the cause of diabetic neuropathy has to be studied in man. The experimental models of diabetes mellitus, although worthy of study in their own right and providing insights into mechanisms which can be tested in man, should not be thought of as models of the human disease. However, in view of the fact that human diabetes mellitus may be of more than one etiology and in view of the fact that there are several types of neuropathy of diabetes mellitus it is not unreasonable to study these experimental models of diabetes mellitus with the view that they might shed light on the mechanisms of

the disease in man.

The specific recommendations that I would favor would be that NIH set aside approximately $4 - $5 million to look into the mechanisms of diabetic neuropathy and its complications. The money might be divided to provide three or four peripheral nerve program project grants, for indi-' vidual grants on diabetic neuropathy, for research fellowships and for the visiting scientist category. It was apparent at the workshop that fruitful collaboration could come from funds being made available to permit a scientist with an ongoing program in research in diabetic neuropathy to visit another center and to conduct research there, utilizing the strength of that other program.

If peripheral nerve centers of study are to be created, the emphasis should be on research. In such centers strength should be demonstrated in several additional disciplines, such as biochemistry, pharmacology, virology, immunology, etc.

Because diabetes mellitus neuropathy is often painful and may result in mutilating acropathy, an important question for investigation would be the pathophysiology of painfulness. An analysis of the factors which make for mutilating acropathy would also provide immediate help. The main support however, of the money set aside for diabetic neuropathy research should be towards understanding the mechanisms of nerve fiber degeneration in diabetic neuropathy using anatomical, pathological, bio-chemical, physiological, pharmacological and immunological techniques.

RECOMMENDATIONS FOR FUNDING AND RESEARCH IN DIABETIC NEUROPATHY

WILLIAM T. NORTON, Ph.D.

The bulk of any earmarked funds should go toward the support of individual grants. Diabetic neuropathy does, however, lend itself to interdisciplinary program-project research. A few, perhaps two or three, such programs should be encouraged. Any more than this is probably unrealistic considering the availability of appropriate interested groups in this country. The obvious variety of the diabetic neuropathies, the probability of multiple pathogenetic mechanisms, and the total lack of agreement on the causes of mechanisms of any of them, points up the need for diverse, creative, and individualistic studies which do not necessarily require the teamwork approach. On the other hand there is a considerable amount of solid data collecting that is required to give all investigators in this field a better foundation. Such work could be more effeciently accomplished by program-project research. The team should include a neuropathologist, a neurologist, a biochemist and the participation or consultation of an immunologist and a virologist. The sort of fundamental information to be obtained from such a study was outlined by Dr. Dyck in his workshop presentation. It would involve a correlative study of such factors as virus infections, histocompatibility types, dietary factors, blood chemistry, natural history of the disease, clinical tests of nerve function, and qualitative and quantitative pathological examination of nerves at autopsy and, if justified, on biopsy samples. Many other program-project approaches could be envisioned but this study seems essential.

Research Possibilities

During the discussions of etiology of diabetes it impressed me, as it evidently also impressed Dr. Tower, how many analogies there are between diabetes and multiple sclerosis (MS). In both there is a possible viral influence, immunologic factors are involved and there is a correlation of the disease with frequency of certain histocompatibility antigens. This is not to imply that the neuropathies of diabetes are akin to the CNS lesions of MS, but that research strategies useful in one disease might be useful in the other. There are undoubtely many other diseases in which this complex of factors is also implicated (i.e. cancer).

In developing a research strategy to look at diabetic neuropathy the neurochemist must decide whether to look at the human disease or certain model systems. If he chooses the human disease he has the option of examining autopsy tissue, nerve biopsy tissue or some easily obtainable tissue non-nervous tissue which may display some generalized metabolic defect such as red cells, lymphocytes, fibroblasts, etc.

The model systems, which include the drug-induced disbetes and various tissue culture systems will of course only permit examination of the effects of lack of insulin and/or hyperglycemia. This is an advantage for the study of these parameters independently of other possible causes, but will not allow accurate investigation of all factors operating in the human diabetic neuropathies.

In either case, whether human nerves or the metabolism and physiology of nerves in animal models are studied, the neurochemist is helped enormously by extensive pathological investigation. The advances in the chemical pathology of neurological disease in the past ten years have all hinged on the pathologists' careful definition of the disease process. This gives the chemist the essential clues which enable him to plan his investigation efficiently. For example if the distal, symmetric, sensory type of neuropathy could be fairly convincingly shown to be caused by ischemic damage, it would be of little interest to neurochemists. (The animal studies indicate that this may not be an adequate explanation).

A specific morphological study that should precede biochemical investigation is a more careful exploration of nerves in the streptozotocin model which show impaired conduction velocity. Although such nerves are presumably morphologically normal, it is possible that subtle changes in either axon or sheath have not been detected. The myelin sheath has tight junctions sealing the lateral loops to each other, and transverse bands sealing the lateral loops to the axolemma. Alterations in these structures could produce a "leaky" sheath with impaired ionic insulation properties, but might be overlooked unless longitudinal sections are examined. Swelling of myelin at the interperiod line could produce a malfunctioning sheath, but such swelling could be masked by shrinkage during processing for electron microscopy. It would however be possible to detect generalized changes in myelin periodicity by low angle X-ray diffraction of fresh nerves. Such subtle changes if found could be indications of a relatively intact but malfunctioning sheath, and might also account for the reversibility of conduction impairment with careful control of blood glucose. The morphological study should also include quantitative counts of neurotubules and neurofilaments, both of which have been implicated in mechanisms of axoplasmic flow.

The studies of Dr. Spritz indicate a general impairment of metabolism of the myelin sheath and, by extrapolation, of the Schwann cell in the streptozotocin model. These studies were possible because purified myelin can be isolated and because there are known specific proteins of the sheath. The major protein subunit of the axonal filament has now been characterized and there are techniques for isolating intact neurofilaments. The filaments and this protein could be used as an axoplasmic marker to follow the metabolism of axon in vivo, as well as its metabolism in vitro in, for example, cultures of the dorsal root ganglion. Of course in vitro metabolism of axonal proteins in isolated segments of nerve, separate from their neuronal perikarya can not be studied. Such a study is an example of an approach which allows

the simultaneous metabolic study of both the Schwann cell and the neuron in experimental models.

A fast growing field in neurochemistry is the development of techniques for isolating specific brain cells in bulk. It is now possible to isolate neuronal perikarya, astrocytes and oligodendroglia and study their biochemical properties separately. It might be possible to apply such procedures to nerve for the isolation of Schwann cells. If such a preparation could be obtained, the insulin response and changes in biochemistry induced by hyperglycemia could be studied directly. These preparations would supplement the Schwannoma cloned lines and ganglion cultures suggested by Dr. Pleasure. Another obvious cuase of neuropathy might be altered axoplasmic transport. Techniques for study of this process were discussed by Dr. Matschinsky. It is also possible to measure flow rates directly in small animals by direct injection of labeled precursors into the spinal cord or ganglion. Flow can be studied either by counting of sectioned nerves or by autoradiography. This process gives actual flow rates which may give different information than that obtained by the suture technique, which measures accumulation of specific enzyme proteins.

If the neuropathies are an expression of a global metabolic defect then other cells and cell membranes might be examined which would give insight into these problems. Such an approach has been used in muscular dystrophy, where it has recently been shown by physical techniques that the red cell membrane is abnormal. This is a bit far afield from neuropathies but does open up possibilities for the study of human diabetes, and avoids the moral and ethical problems associated with nerve biopsy. Genetic defects are expressed in all cells. Cultured fibroblasts, for example are now routinely used for diagnosis of the sphingolipidoses, the use of such tissues could clarify the relative importance of genetics vs. toxicity of hyperglycemia (or lack of insulin) in the controversy concerning the relationships of glucose, sorbitol, inositol and phosphatidyl inositol metabolism.

I have already discussed some possible studies of myelin in experimental models. Chemical studies of myelin in human neuropathies will probably be relatively uniformative. Many demyelinating diseases of the CNS yield myelin of abnormal composition. This probably represents myelin in the process of breaking down. Dr. Spritz has examined PNS myelin from human diabetics and found no alterations in composition. There are many differences between central and peripheral nervous system myelin, but do these have any importance in explaining diabetic neuropathy and the absence of brain changes (other than caused by vascular pathology)? There are many causes of demyelination, including mechanical, genetic, nutritional, toxic, infectious, and allergic. If any of the neuropathies actually involve segmental demyelination (and not Wallerian degeneration secondary to axonal damage) then any of the last five of these etiologies seems a

possibility for serious consideration. Again I would stress that the pathologist must furnish more information before it would seem profitable for the chemist to begin on any direct study of human diabetic neuropathy.

CELLULAR DIVERSITY AND AXOPLASMIC FLOW AS FACTORS IN THE PATHOGENESIS OF DIABETIC NEUROPATHY

Franz M. Matschinsky, M.D.

Both the central (CNS) and the peripheral nervous system (PNS) must be considered when trying to elucidate the pathogenesis of diabetic neuropathy. One of the major difficulties in this undertaking is the bewildering regional and cellular diversity of the nervous system. Studies undertaken so far as to the possible molecular mechanism of the hypogly-cemic syndrome are a striking example to this point. It has been re-peatedly demonstrated that the ATP and P-creatine levels of average brain or even of various major regions of the brain are unaltered in severe acute hypoglycemia in experimental animals. It has now also been dem-onstrated that the levels of certin amino acids possibly functioning as neurotransmitters are not affected in the average brain.

The hypoglycemic syndrome may however arise from hypoglycemic energy deprivation or amino acid losses of a fraction of cells in the brain stem, for example. Such cells may be particularly sensitive to glucose depriva-tion but might contribute only a small percentage of the total brain mass. Quantitative histochemical methods need to be applied in a systematic fashion to explore such a possibility. Even the most complex structures of the CNS can now be studied at the microscopic level. Contents of crucial intermediates and cofactors of metabolism, of transmitter amino acids, and of ATP and P-creatine can be determined in microscopic samples. This has been documented by systematic studies of the three dimensional distribution of GABA, glycine, aspartate and glutamate and of the enzymes acetylcholinesterase and choline acetylase in the intricate structure of the cochlear nucleus of the cat and the rat and has also been shown to be feasible in preliminary measurements in the hypothalamus of the rat. This biochemical approach promises to become as powerful a probe of the cellular diversity as electrophysiological techniques. And it might be particularly useful in studying the biochemical basis of the hypoglycemic syndrome (Table 1). The approach may also become useful in studying peripheral nerves at the histological level.

Table 1

SOME POSSIBLE APPROACHES TO ELUCIDATE BIOCHEMICAL MECHANISMS OF
HYPOGLYCEMIC COMA

1) Comprehensive study of microscopic distribution of the energy reserces in the CNS during hypoglycemia with particular emphasis to the brain stem and the hypothalamus.

2) Comprehensive reinvestigation of the refueling capacities of sugars and sugar analogous (e.g. glyceraldehyde) in hypoglycemia.

3) Tracing of preferred pathways of glucose and glucose analogue usage following hypoglycemia.

4) Use the layered structure of the retina as a model of the hypoglycemic CNS, since certain neuronal elements (i.e. mitochondria, nuclei and synaptic complexes) can be studied in pathological in vivo settings.

In order to understand the pathogenesis of the diabetic PNS neuropathy all conceivable morphological and functional aspects of the PNS have to be considered. One of these is the role of the bidirectional axoplasmic flow. A systematic study of this aspect of diabetic nerve has not been performed. Therefore, in a first approximation orthograde axoplasmic transport of cholinesterase and choline acetylase was measured in the sciatic nerves of normal as well as treated and untreated streptozotocin diabetic rats. In vivo accumlation of the two enzymes proximal to a tie was used as a measure of axoplasmic flow. Such measurements were performed three to four weeks after inducing insulin treatment with a fixed dose of an intermediate insulin. Accumulation of both enzymes was decreased, cholinesterase by about 20% and choline acetylase by about 40%. Insulin treatment eliminated the defect (Table 2). The experiment was performed on three different groups of animals with comparable results. Only further research will show whether the axonal change observed here is not merely an expression of severe dehydration, uremia, or other alternations typical for the acute experimental diabetes in animals. It is also not yet clear whether this finding has any significance for diabetic neuropathy in man.

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Table 2

ORTHOGRADE AXOPLASMIC FLOW OF CHOLINESTERASE AND CHOLINE ACETYLASE
IN SCIATIC NERVE OF DIABETIC RATS

Condition	Accumulation (10^{-9}moles/hr)		
	Expt. I	Expt. II	Expt. III*
Controls	202 + 14 (6)	158 + 8 (10)	372 + 17 (12)
Diabetics	159 + 10 (−21%) (6)	123 + 9 (−22%) (10)	292 + 18 (−21%) (16)
Treated Diabetics	− −	145 + 6 (−8%) (14)	402 + 9 (+8%) (12)
	Choline Acetylase		
Controls	−	8.05 + 1.10 (10)	6.25 + 0.66 (12)
Diabetics	−	5.21 + 0.66(−35%) (10)	3.67 + 0.47(−41%) (16)
Treated Diabetics		7.80 + 0.66(−3%) (14)	7.02 + 0.47(+12%) (12)

* In Expt III a radiometric assay for cholinesterase was employed
with acetylcholine instead of acetyl-thiocholine as substrate which was
used in Expts. I and II.

From these preliminary results it would seem that the detailed study of
axoplasmic flow by various approaches might be rewarding. Several initial
specific aims come to mind (Table 3). It would also seem rewarding to
initiate studies of axonal flow in various genetically diabetic animals,
both of the obese hyperglycemic variety and ketotic hyperglycemic variety.

Table 3

SOME APPROACHES TO ASSESS THE POSSIBLE INVOLVEMENT OF ALTERED
AXOPLASMIC FLOW IN THE PATHOGENESIS OF DIABETIC NEUROPATHY

1) Apply various approved methods currently used in the study of
   orthograde and retrograde axoplasmic flow in vivo to assess
   whether there is indeed altered flow in somatic and autonomic
   nerves in experimental diabetes.
2) If axoplasmic flow is altered study the time course of development
   and the possible reversibility by insulin treatment.
3) Evaluate various in vitro methods for studying diabetic impairment
   of axoplasmic flow and possible effects of insulin on flow in vitro
4) Find out whether the decreased axoplasmic flow in diabetic rats is
   in any way related to altered MNCV, as seen in certain stages of
   experimental diabetes.
5) Formulate working hypotheses explaining the apparent defect in axo-
   plasmic flow (i.e. energy deficit, altered ionic gradients, loss
   of effector molecules, accumulation of inhibitors and other
   possibilities).

David Pleasure, M.D.

The clinical and pathological features of diabetic mononeuritis, autonomic neuropathy and symmetrical distal polyneuropathy were reviewed by other participants in the recent workshop at the Americana. Despite careful electrophysiological and pathological studies, no consensus has been reached as to whether Schwann cells or neuronal elements are primarily affected in any of these forms of neuropathy. Ischaemia, trauma, hyperglycemia and insulin deficiency are all likely to have etiological importance, but the pathogenesis of diabetic neuropathy remains obscure.

Pfeiffer and Tanzer have reported on the biochemistry of cloned neoplastic Schwann cells. The cells actively synthesized a basement membrane form of collagen, suggesting that endoneurial basement membrane is of Schwann cell origin. In addition, one clone of Schwann cells synthesized a basic protein resembling that in myelin, despite the absence of neuronal elements in the cultures. Schwann cell cultures such as these provide an ideal opportunity to establish whether glucose transport and phosphorylation in Schwann cells are insulin-dependent, and whether plasma membrane lipid and protein synthesis is adversely affected by hyperglycemia, ketosis, or insulin deficiency.

Short-term in vitro incubations of peripheral nerves, as described by Spritz, and tissue culture of dorsal root and sympathetic ganglia, permit study of interactions between Schwann cells and axons. Globus et al., and Lasek et al., have demonstrated transfer of amino acids and proteins from Schwann cells to axons in invertebrates, and similar studies be carried out in higher animals. The demonstration of a trophic role of Schwann cells in the maintenance of unmyelinated axons might be of importance in the pathogenesis of diabetic autonomic neuropathy. Conversely, in vivo studies have suggested that axons can provide a trophic signal inducing the synthesis of myelin by any Schwann cell, even one in an usually unmyelinated nerve. Dyck has pointed out that segmental demyelination does not necessarily imply primary Schwann cell dysfunction, but may, instead, result from a failure of this trophic axonal influence.

Studies of CNS have shown that 3-hydroxy-3-methylglutaryl coenyzme A reductase and fatty acid synthetase, rate-limiting in cholesterol and fatty acid synthesis respectively, are under fundamentally different control than in non-neural tissues. For example, both these enzymes are rapidly induced in liver and fibroblasts by lipid deprivation, whereas in brain, lipid deprivation does not change enzyme levels, or even represses them. Since these pathways are vital in myelin synthesis, the effects of metabolic derangements that occur in diabetics on the levels of these enzymes in peripheral nerve may be of importance in understanding diabetic neuropathy.

Though careful epidemiological, clinicopathologic and electrophysiological studies of diabetic neuropathy are of importance, it is my own bias that biochemical investigations of the properties of Schwann cells, and of the trophic interactions of Schwann cells with axons are an essential step in the eventual prevention or rational treatment of diabetic neuropathy.

DIABETIC NEUROPATHY
David Pleasure, M.D.

That neuropathy occurs in patients with diabetes mellitus was first recognized almost 200 years ago. Until 100 years ago, it was generally thought that the neuropathy caused the diabetes. We now recognize that neuropathy is a complication of diabetes, often causing severe discomfort and disability, but we remain uncertain as to the pathogenesis of diabetic neuropathy, and have no uniformly effective way to prevent nerve damage or reverse its progression.

There are 3 clinical patterns of presentation of diabetic neuropathy:

1. .loss of strength and sensation in the distribution of one or more discrete peripheral or cranial nerves (mononeuritis, mononeuritis multiplex).

2. impaired blood pressure regulation, gastrointestinal function, and sexual potency (autonomic neuropathy).

3. symmetric distal loss of sensation, reflexes and strength, usually most severe in the feet, sometimes associated with foot and leg pain (symmetric distal sensorimotor neuropathy).

Diabetic mononeuritis and mononeuritis multiplex most frequently affect the femoral, sciatic, median, ulnar, and oculomotor nerves. Onset is often acute, frequently with pain. Electrophysiological studies show localized dysfunction in affected nerves, but often reveal subclinical involvement of other nerves as well. Recovery is sometimes rapid, and does not depend upon good control of plasma glucose. In some patients, pathological studies have shown occlusion of an intraneural artery, resulting in insufficient blood supply to the affected nerve. In other patients, mononeuritis is the result of local trauma to the nerve at a vulnerable point (eg, median nerve at the wrist, ulnar nerve at the elbow).

Diabetic autonomic neuropathy is usually of insidious onset, presenting with unstable blood pressure, diarrhea or other gastrointestinal disturbance, and diminution in sexual desire and potency. A variety of therapies help to improve blood pressure control in patients with autonomic neuropathy, but there are no effective measures for the treatment of the sexual dysfunction. Pathological studies reveal degeneration and death of neurons in the autonomic ganglia, and loss of axons in autonomic nerves. The pathogenesis of diabetic autonomic neuropathy is unknown.

Symmetric distal sensorimotor neuropathy is the most frequent form

of diabetic neuropathy. Many diabetics show only loss of ankle reflexes and of vibratory sensation in the toes, but others may develop unbearable leg pain and severe wasting and weakness of foot and shin muscles. Electrophysiological studies often show slowing of the rate of conduction of nerve impulses, particularly distally in the legs, and there is evidence that close control of plasma glucose levels in patients with early symmetric distal sensorimotor neuropathy sometimes reverses both the electrophysiological and the clinical manifestations of nerve dysfunction. Pathological studies demonstrate either selective loss of small myelinated and large unmyelinated axons (particularly in younger patients with painful feet), or breakdown of myelin with sparing of axons ("segmental demyelination") (particularly in older patients). The pathogenesis of diabetic symmetric distal sensorimotor neuropathy is unknown, but nerve degeneration probably results from hyperglycemia or insulin deficiency, rather than from occlusive vascular disease.

A number of animal models that simulate diabetic symmetrical distal neuropathy are available. Animals made insulin deficient by administration of a pancreatic islet cell toxin (alloxan or streptozotocin) or by pancreatectomy develop clinical and electrophysiological features of diabetic neuropathy, though there are no consistent pathological alterations in the peripheral nerves. Segmental demyelination has been found in the peripheral nerves of a strain of Chinese hamsters with genetically determined diabetes mellitus.

The application of quantitative histological and biochemical techniques to nerves from diabetic animals, and from patients with diabetic neuropathy, may yield answers to several central questions about the pathogenesis of this diabetic complication:

1. What is the role of insulin in the metabolism of peripheral nerve?

2. Are Schwann cells damaged as a direct consequence of hyperglycemia or insulin deficiency, or does segmental demyelination occur as a result of axonal dysfunction?

3. Why are diabetic nerves more susceptible to trauma than normal?

4. Is there any pathogenetic significance to the accumulation of sorbitol and fructose in diabetic nerve?

5. Are there abnormalities in the synthesis of phospho-inositides and of basement membrane glycoproteins in peripheral nerve, as reported in other tissues? Does the myelin glycoprotein synthesized by Schwann cells from diabetic nerve contain a normal spectrum of sugars?

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RELATIONSHIP OF INSULIN DEFICIENCY, HYPERGLYCEMIA, AND ALTERATIONS IN MYOINOSITOL METABOLISM TO THE PATHOGENESIS OF IMPAIRED PERIPHERAL NERVE CONDUCTION VELOCITY IN EXPERIMENTAL DIABETES.

ALBERT I. WINEGRAD, M.D.

Newly diagnosed juvenile diabetics who lack symptoms or objective evidence of peripheral neuropathy on standard neurological examination have been reported to consistently exhibit widespread alterations in peripheral nervous function when studied by sensitive electrophysiological techniques; the latter include decreased peripheral motor and sensory nerve conduction velocities. The morphological changes, if any, present in the nerves of newly diagnosed juvenile diabetics have not been examined in a systematic fashion. The initiation of insulin therapy has been reported to result in some improvement in NCV but the differences in NCV in juvenile diabetics and normals increase with increasing duration of disease. It has been speculated that the alterations in NCV present in newly diagnosed juvenile diabetics may reflect the chronic metabolic derangement presently believed to condition the development of specific forms of diabetic peripheral neuropathy. Recent studies have clarified the relationship of insulin deficiency and hyperglycemia to the development of impaired MNCV in rats with experimental diabetes. Impaired sciatic MNCV consistently develops within two weeks after the administration of streptozotocin but only in animals who become persistently hyperglycemic; a similar alteration is known to occur following pancreatectomy or the induction of alloxan diabetes. Previous workers were unable to prevent the development of impaired sciatic MNCV in rats with experimental diabetes by insulin treatment, or to affect it by the addition of insulin to the isolated nerve in vitro. As detailed in a recent publication (J. Clin. Invest. 55: 1326, June 1975) insulin treatment which results only in the maintenance of normal weight gain and a decrease in the degree of hyperglycemia does not prevent the development of impaired sciatic MNCV; however, insulin treatment which obviated any prolonged period in which the plasma glucose level exceeded that found in normal subjects consistently prevented the development of impaired MNCV. Thus, the development of impaired MNCV in experimental diabetes appears to be a consequence of insulin deficiency and/or hyperglycemia although this relationship has been obscured for almost 10 years. (It is of note that normalization of plasma glucose fluctuations in human diabetics is not achieved in the vast majority of patients irrespective of the form of therapy presently employed; this point has been documented in a number of recent studies.)

Experimental diabetes has been found to result in a derangement in the regulation of the concentration of free myoinositol in the peripheral nerve of rats which correlates with the development of impaired MNCV; peripheral nerve normally maintains free myoinositol (MI) concentrations

60-90 fold higher than that of plasma although the extent to which this results from endogenous synthesis and/or active concentration is unknown. Streptozotocin diabetes results in a decrease in the free MI concentration in rat sciatic nerve, and insulin treatment which prevents the development of impaired MNCV prevents this decrease, whereas insulin treatment which is ineffective in preventing impaired MNCV also fails to prevent the decrease in nerve free MI concentration. Free MI is a precursor for the synthesis of phosphatidylinositol and the latter is the parent compound of the polyphosphoinositides (DPI and TPI) which are present in significant concentrations in peripheral nerve and are known to be primarily associated with myelin in brain. (There remains significant controversy over the suggestion that the rapid turnover of specific inositol containing phospholipids may be functionally related to the conduction of the neural impulse as suggested by Hawthorne and co-workers.)

Human and experimental diabetes are associated with marked increases in urinary free MI excretion but without significant alteration in plasma free MI concentrations. Since there is no established dietary requirement for free MI in normal humans or rats little significance has been attached to this urinary loss of free MI. The concentration of free MI in the nerves of normal rats was found to be subject to acute alterations by increases in plasma free MI concentration suggesting that elevated plasma free MI concentration within a specific range resulted in an increase in active concentration. Pharmacological supplementation of the diet with 1.0% free MI resulted in plasma free MI concentrations of approximately 0.20 mM in normal and streptozotocin diabetic rats; under these conditions the normal and diabetic rats maintained similar elevated nerve free MI concentrations and despite severe persistent hyperglycemia in the diabetics the development of impaired MNCV was modified or totally prevented. Dietary free MI supplementation of the same degree was also found to reverse the impaired MNCV in diabetic rats in whom it was permitted to develop on a standard diet containing all known rat dietary requirements. The effects of increased dietary free MI appeared to be unrelated to alterations in the concentrations of glucose, sorbitol, or fructose in peripheral nerve. The development of impaired MNCV in experimental diabetes appears to be primarily a consequence of insulin deficiency and/or hyperglycemia but appears to be mediated in part via an alteration in the metabolism of free MI which is subject to modification by dietary free MI intake and also be renal disease which affects plasma free MI concentration. These factors have not been previously considered in efforts to develop an appropriate model for overt distal symmetrical polyneuropathy in animals with experimental diabetes.

At present there is little if any direct contact between the groups with diverse disciplinary backgrounds who are engaged in research related to the diabetic neuropathies. The workshop held in New York City provided a unique and valuable opportunity for the exchange of ideas and for the development of collaborative efforts. An annual meeting of this type would provide a valuable means of insuring that the work in this area proceeded

with an appropriate recognition of developments in fields unrelated to the workers primary discipline.

The manner in which insulin deficiency and/or hyperglycemia affect peripheral nervous metabolism and function deserves increased attention since there is now evidence that these are primary factors in the development of impaired MNCV and impaired axonal transport in experimental diabetes.

The morphologic and biochemical basis of the alterations in peripheral nervous function found in newly diagnosed juvenile diabetics deserves increased attention since these may reflect the alterations that condition the development of irreversible pathology found in association with overt diabetic polyneuropathy.

Research support for an effective program concerned with the pathogenesis and prevention of the diabetic neuropathies is required; this must recognize the need for a multidisciplinary approach and the problems which this entails with the limited personnel resources in this area and in most medical institutions. In addition to Centers in the few areas where there is a concentration of qualified investigators there is a need for effective means to encourage and support collaborative efforts by investigators located in different institutions; the latter must include some means frequent personal interaction.

SEARCH FOR A VASOPROLIFERATIVE FACTOR IN
PROLIFERATIVE DIABETIC RETINOPATHY

Elmer J. Ballintine, M.D.

Several clinical observations support the inference that a humoral or locally diffusible substance is an important participant in the development of ocular neovascularization and especially in diabetic retinopathy. Among these are the observations that ocular vascular disease in the posterior part of the eye, for example, occlusion of the central retinal vein and diabetic retinopathy, is frequently followed by iris neovascularization. Certain observations on the pathogenesis of retrolental fibroplasia suggest that some of the proliferative phases may be stimulated by a locally acting agent. In eyes having retinoblastoma, neovascularization of the iris occurs frequently, without any obvious connection to the tumor in the posterior region of the eye.

In the immediate post-operative period vitrectomized eyes occasionally exhibit a rapid development of dilated vessels and neovascularization on the anterior surface of the iris which seems to occur more quickly if the lens has also been removed. This neovascularization then may disappear over a period of several weeks. These observations all suggest that a substance produced in the posterior portions of the eye may diffuse into the anterior portions and stimulate neovascularization of the iris. This same factor may participate in retinal neovascularization.

The demonstration by Folkman, Gimbrone and others of a tumor angiogenic factor that produces neovascularization in iris and cornea emphasizes the possibility that neovascularization in the eye may be the result of more than one diffusible factor.

In the past four years the development of surgical techniques for removing the diseased vitreous humor from human eyes in which severe reduction in vision is mainly the result of persistent vitreous hemorrhage has, for the first time, made available vitreous humor from eyes with proliferative diabetic retinopathy in large enough quantities to make a systematic search for vasoproliferative properties possible.

At the Clinical Branch, NEI, Dr. Daniel Eichenbaum, Dr. Steve Charles, and Dr. Ralph Helmsen have undertaken the isolation of a vasoproliferative factor from the vitreous washings from the eyes of diabetic patients who have undergone vitrectomy. While their experiments are not conclusive, the preliminary results are encouraging.

In most of the vitrectomy operations the volume of the vitreous aspirate and washings was 150 ml. or less. These were either processed immediately or kept frozen until they could be pooled with other specimens. The main emphasis was on the isolation of the protein component. In most experiments the aspirate was filtered through a .45 MU millitex filter to remove particulate matter, through an Amicron filter that retained proteins of 10,000 molecular weight or greater. The retained protein was washed with .01 molar sodium chloride solution and the volume of the protein solution was reduced to about 15 ml. One milliliter alliquots were then lyophylized and stored.

The lyophylized alliquots were assayed by reconstituting them in .4 ml. of water. Each alliquot contained 3-6 milligrams of protein. Several assay procedures were considered but rejected because they lacked sensitivity. The corneal pouch assay as developed by Gimbrone and associates was adapted to this work. In this assay a superficial pouch is made in the stroma of the rabbit cornea extending to within two millimeters of the limbus inferiorly. In the pouch is placed an alliquot of the vitreous fraction or a 20 percent concentration of the reconstituted alliquot in a pellet of 7 percent polyacrylamide gel. Forty-two corneal assays, 23 using vitreous fractions and 19 blank controls were performed using seven different vitreous specimens from eyes having some form of proliferative retinopathy.

These assays were encouraging in that in three of the pockets specific neovascularization was observed and a nonspecific inflammatory neovascularization in only one. Among the saline controls there were five neovascular responses and eight nonspecific vasoproliferative responses accompanying inflammation. It was judged that under the conditions of the experiment the assay was difficult to interpret and did not discriminate sharply between nonspecific inflammatory responses and a specific vasoproliferative response.

A second attempt to develop a suitable assay was the injection of reconstituted alliquots of the processed vitreous into the vitreous cavity of the owl monkey. This eye was chosen because the owl monkey has a fluid vitreous which might permit free diffusion of the vaso-proliferative factor to a responsive site. Four specimens of vitreous humor either from a single eye or from pooled vitreous aspirates were assayed. A positive result was the appearance of what was judged to be neovascular proliferation on the iris. In no eyes was a proliferative response seen in the retina.

A vasoactive response was seen on the iris in two of three eyes injected with specimen number one, one of two eyes in specimen number two, and two of two eyes in specimen number four. Lyophylized alliquots of specimen number one were reassayed six months later and a positive response observed in one of three eyes.

The owl monkey eyes having a vasoproliferative response as judged by slit lamp examination were examined histologically. In only two specimens was there undoubted neovascularization of the iris by histologic criteria. These experiments, therefore, cannot be said to have demonstrated unequivocally the presence of a vasoproliferative factor but they have encouraged us to continue the work.

A number of possibilities remain to be explored. The preliminary experiments used only the high molecular weight protein fractions and it is possible that low molecular weight substances or other polymers such as mucopolysaccharides are the active substance. Several techniques for fractionation should, therefore, be investigated.

Effective work on isolation and characterization of the factors will depend upon an improved assay. Some of these might involve the use of slow release from plastic investments or absorptions, anoxic sensitization of the test animal, and improved techniques for implantation in various parts of the eye, both vascular and nonvascular.

Development of assays using tissue culture should be undertaken. Stimulation of vessel growth in embryonated eggs, stimulation of growth in culture of retinal capillary endothelial and mural cells and stimulation of labelled thymidine incorporation into these cells are likely possibilities.

Still unexplored is the possibility that neovascular growth on the retina is the result of failure of normal inhibition of vascular growth by the internal limiting membrane or some component of the vitreous humor.

SUMMARY OF PRESENTATION ON
DIABETIC RETINOPATHY

David G. Cogan, M.D., and Toichira Kuwabara, M.D., Ph.D.

Diabetic retinopathy is picturesquely described as "red spots and white spots" when viewed with the ophthalmoscope. The red spots are a mixture of hemorrhages and microaneurysms that are clinically distinguishable only by fluoroangiography. Unlike other types of hemorrhagic retinopathy they predominate in the central or perivascular fundus and are predominantly punctate instead of flame-shaped. The white spots consist chiefly of exudate situated also in the central area and frequently having a cluster distribution. They are punctate, although confluent, and are yellowish instead of white. They are to be distinguished from the white cotton wool spots which are characteristically minimal in uncomplicated diabetic retinopathy.

The histopathogenesis of intra-retinal retinopathy in diabetes appears to be the following sequence of events: loss of mural cells leading to loss of capillary tone; consequent dilatation and micro-aneurysmal outpouching; consequent formation of arteriolo-venular shunts with ischemic foci by by-passed capillary bed; hemorrhage, transudatation ("exudates"), and macular edema from the distended vessels.

The histopathogenesis of proliferative retinopathy in diabetes is less readily explained but any hypotheses must account for the initial rupture of the internal limiting membrane. Once the vessels have perforated this membrane the proliferation into the vitreous appears to be a nonspecific and secondary phenomenon analogous to granulation tissue elsewhere.

In accordance with the foregoing, future research should encompass:

1) further studies on the histochemistry and electron microscopy of the mural cells and endothelium in the normal and diabetic capillaries (including comparison with other types of vascular retinopathy), and

2) initiate comparative studies on the chemical and mechanical vulnerability of the internal limiting membrane in diabetes.

Most important is the attraction of creative investigators with histochemical and immunological sophistication into the field of diabetic research and to indoctrinate physiologists and immunologists with the unique opportunities offered by study of the retinal circulation.

RECOMMENDATIONS REGARDING RESEARCH IN DIABETIC RETINOPATHY

M. D. Davis, M.D.

In my opinion, there are three areas of research to which the Commission should give special consideration:

1) animal models which develop microvascular complications comparable to those of human diabetes,

2) randomized clinical trials of agents which may ameliorate vascular complications, and

3) clinical research in well selected groups of patients with varying degrees of diabetic retinopathy and varying durations of (insulin dependent) diabetes, aimed at applying new methods, such as measurements of blood flow and oxygen saturation, to the elucidation of the pathogenesis of the retinopathy.

The long periods of time and high levels of funding required by investigations of these types make it unlikely that they will be pursued vigorously unless they are identified and supported as areas of special emphasis.

The work of Engerman and Bloodworth has demonstrated that retinopathy and probably nephropathy identical to the milder stages of that seen in human diabetics can be produced experimentally in dogs by five years of alloxan diabetes. Similar findings in a very small group of rhesus monkeys after eight to ten years demonstrate that, with enough time, manpower, patience and money, it will be possible to carry out the critical experiments requiring invasive techniques not permissible in man that will probably be necessary for an understanding of pathogenesis.

None of the three large-scale clinical trials currently underway deals with the patients most likely to provide fundamental insight into pathogenesis or to be greatly benefited by new therapeutic interventions. The Diabetic Retinopathy Study and the Diabetic Retinopathy Vitrectomy Study both are concerned with evaluation of the efficacy of local ocular treatment (photocoagulation and vitrectomy) in patients with advanced retinopathy. The University Group Diabetes Program is limited to the study of the possible effect of diabetic control on vascular complications in non-insulin dependent patients.

I believe it would be of great interest to carry out a study in insulin dependent patients that would combine assessment of two different levels of effort made towards "good" control with a trial of one or more

drugs, such as aspirin, an aldose reductase inhibiter, or calcium dobesilate, which offer hope of reducing vascular complications by some mechanism other than improvement of control. I should like to suggest that the Commission consider recommending the establishment of a Steering Group to consider treatments which should be tested in such a collaborative clinical trial. A small number of clinical centers might be established a year or so later to get recommended trials underway, with additional centers joining a year or two after that. In my opinion, drug trials should be combined with a trial of two levels of "control" in insulin dependent patients. One level, currently advocated by many physicians, generally limits insulin to one injection daily, aims at avoidance of acidosis and hypoglycemia with the acceptance of asymptomic glycosuria, and emphasizes minimizing the psychological stress which may result from regimentation of the patient's daily activities. The other level, coming more into favor recently, relies upon multiple daily injections of insulin and aims for negative urine sugars at all times and blood sugars near normal much of the time. I believe risks and benefits are balanced, and that such a trial would be ethical in thoroughly informed patients. If the extra effort and regimentation of the patient's life style required by management which aims at coming as close as possible to normoglycemia really does reduce the incidence and severity of vascular complications, many patients would choose such management. If the difference in vascular complications between such management and that which aims only at the much more easily achievable goal of freedom from symptoms of hyper and hypoglycemia is trivial, however, few would. Our patients are as eager as we are for a well documented answer to this question, which they must face every day of their lives. Only if patients and physicians join together as a team in a randomized trial will such an answer be obtained.

The prevalence of minimal retinopathy, when judged with the sensitive method of stereoscopic fundus photography, is sufficient even at five to seven years duration of diabetes to allow a decrease secondary to treatment to be detected (data on file from Commission meeting on pathogenesis of vascular complications).

If three groups of insulin dependent patients with different durations of diabetes were included in the trial, the results from the various groups after five to seven years might be used to decide whether to modify the protocol. For instance, if, in the group entering the study soon after diagnosis and randomized to "loose" control, the prevalence of very early retinopathy (a small number of microaneurysms only) six years after entry was substantially greater than in patients in the "tight" control group, consideration would have to be given to advising those patients in the "loose" control group who were willing to do so to change to tight control. If we knew that continued "loose" control in these patients would be attended by progression to more severe retinopathy (and probably nephropathy) with

substantially greater frequency than would be the case with a change to tight control, we would be likely to give such advice, but this, of course, may not be the case. During the first six years of the study we could obtain information on this question by including two additional groups of patients, with five to seven and ten to twelve years duration, respectively, at entry, in whom previous management had approximated the "loose" control described above. Random assignment of these patients to the two levels of control could be expected to give us further information to help with the decision regarding a protocol change for the first group of patients.

Under the proposed protocol there are several ways in which patients in the trial might benefit from it and I believe it would appeal to thoroughly informed patients.

Another major advantage of a long-range ongoing collaborative trial of the type proposed would be the availability of this population for trials of new therapeutic agents in the future and for studies seeking to improve our understanding of pathogenesis. When a new technique, such as measurement of retinal blood flow or oximetry of the blood in retinal vessels, is perfected, its developers could go to several of the collaborating centers with their apparatus for periods of several weeks to collect data in large numbers of carefully selected patients with good documentation of duration, past management and vascular status. For instance, recently diagnosed patients could be compared with those of five to ten years duration, the latter group subdivided on the basis of presence or absence of retinopathy, management regimen, etc.

ANIMAL MODELS OF DIABETIC RETINOPATHY

Ronald L. Engerman, Ph.D.

In spite of widespread research interest in the problem of diabetic retinopathy, the pathogenesis of this condition has remained poorly understood, and no reliable means of preventing or arresting the retinopathy has yet become available. A serious obstacle to progress in this area has been the scarcity of animal models suitable for study of the retinopathy.

Animal models which are available for laboratory investigation of the retinal lesions of diabetes may be divided into either of two types. In one, the animal is experimentally or spontaneously diabetic and the ocular changes observed are identifiable with the metabolic and/or genetic characteristics of diabetes. This type of model is the more familiar of the two, and is the subject of the following discussion. Nevertheless, it is useful to acknowledge an alternative type of model, one in which the animal is not diabetic but in which the lesions occurring are morphologically analogous to those of diabetes. Among the latter models which may prove relevant to diabetic retinopathy are retinal, vitreal, and/or vascular changes which have been produced for example by intra-arterial injection of minute glass or latex beads, by intra-ocular implantation of angiogenic tumors or products, by feeding sucrose-enriched diets, etc. Additional models of either type, and further studies of the models reported are badly needed.

Published reviews occasionally leave an impression that diabetic retinopathy has been clearly produced many times and in several species (cf. Caird, Pirie and Ramsell: Diabetes And The Eye). Unfortunately, only in diabetic dogs has a retinopathy been identified which is both morphologically acceptable and consistently reproducible. The retinopathy in dogs was discovered in spontaneous diabetes and subsequently was reported in metapituitary diabetes and in alloxan diabetes.

Capillary aneurysms, an early and characteristic component of diabetic retinopathy, are known to occur also in alloxan diabetic rhesus monkeys. Although aneurysms have been reported by Gibbs and coworkers at two to four years of diabetes in such monkeys, aneurysms have occurred only after seven or more years of chronic glucosuria in alloxan diabetic rhesus monkeys in our laboratory. Since cataractogenesis in alloxan diabetes seems less rapid in monkeys than in dogs (and less rapid in dogs than in rodents), it is feasible to investigate clinically a number of retinal lesions (e.g., capillary aneurysms, vaso-obliteration, cotton wool spots, macular edema, macular ischemia).

Study of the retinopathy in monkeys presumably will require durations of diabetes even greater than the approximately five years seemingly necessary in dogs.

Studies of rodents, rabbits, and other animals seem not to have proven as productive. If capillary aneurysms do indeed occur in diabetic rodents and other animals, that fact remains to be demonstrated in a convincing fashion. However desirable it may be to identify an animal model which is less expensive and more convenient than the experimentally diabetic dog, very long term studies of such large animals remain essential at the present time.

PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

Ronald L. Engerman, Ph.D.

Efforts to investigate the pathogenesis and treatment of diabetic retinopathy have been impeded by the lack, in past years, of an acceptable model of the retinopathy in animals made diabetic experimentally. A variety of retinal lesions continue to be reported in animals made diabetic by means of pancreatectomy, or by the administration of alloxan, streptozotocin, or various hormones. Only in diabetic dogs have such lesions proven to date to be reproducible and morphologically comparable to the retinopathy observed in diabetic patients.

Retinal capillary aneurysms and other microvascular lesions typical of diabetes mellitus in patients have been shown to develop in dogs made diabetic by means of either alloxan or growth hormone. Retinopathy in the dog appears to depend little if at all upon the means by which the deficient insulin activity has been induced, and identical retinal lesions occasionally have been described also in dogs in which the diabetes has developed spontaneously. Retinopathy in the dog is, however, highly dependent upon the duration of diabetes, and rarely has appeared until after many months (three or more years) of diabetes. Pathogenetic mechanisms which may account for the lengthy interval between the induction of diabetes and the apparent onset of retinopathy are as yet not well understood, but presumably are fundamental to the ensuing retinopathy. At the present time long term studies seem to be essential.

In an attempt to determine whether or not retinal and other complications of diabetes may be inhibited by careful treatment with commercial insulin, dogs have been made alloxan diabetic and randomly distributed into either of two prospective treatment groups. In one group it was intended that the metabolic signs of diabetes be controlled poorly, and commercial insulin was administered in doses inadequate to prevent chronic severe hyperglycemia and glucosuria. In the other group it was intended that the metabolic disorder be controlled well, and the animals received food and commercial insulin twice daily such that the glucosuria became mild and infrequent. Animals of the latter group remained sugar-free up to 51 days per 100 days throughout the five-year period of study. Experimental improvement of the carbohydrate disorder was accompanied by an amelioration of hyperlipemia and other clinical signs of deficient insulin activity. By 60 months of diabetes, retinal capillary aneurysms, pericyte ghosts, obliterated vessels, and other microvascular abnormalities typical of diabetes were apparent in each animal of the Poor Control group. Good control was found to result in a significant reduction of the incidence and severity of retinopathy.

Ultrastructural studies on renal glomerular lesions and capillary basement membrane width in the animals are in progress in the laboratory of Dr. James Bloodworth, and the data seem consistent with the apparent inhibition of retinal microvascular disease in the Good Control group.

The evidence available suggests (1) that the mechanism responsible for diabetic retinopathy is not peculiar to hereditary diabetes, and may be initiated instead as a result of deficient insulin activity, and (2) that the development of retinal and other microvascular complications of diabetes may be inhibited by careful control of the metabolic disorder with commercial insulin.

SUMMARY OF PRESENTATION ON DIABETIC RETINOPATHY

Robert N. Frank, M.D.

One of the most important observations of recent years in the study of diabetic retinopathy has been the finding of Drs. Kuwabara and Cogan that the mural cells, or intramural pericytes, of the retinal capillaries are selectively lost relatively early in the disease, before the development of the more extensive retinal vascular abnormalities that directly cause visual loss. Because our knowledge of the biochemistry and function of retinal vascular cells is so slight, the relationship between mural cell loss and the later events of diabetic retinopathy has never been clarified. Nor have we any idea of the differences between mural cells and endothelial cells that make the former so much more fragile in diabetes. In the hopes of learning more about the growth, biochemistry, and function of retinal capillary cells, Dr. Sheldon Buzney and I have placed capillary fragments from rhesus monkey, cattle, and human retinas in tissue culture medium and studied their behavior. The capillaries were isolated by gentle homogenization and filtration on nylon mesh sieves according to the method of Meezan, Brendel, and Carlson. Within a few days the capillaries curl up and form tight, amorphous masses on the culture plate. PAS-stained preparations at this point reveal masses of basement membrane material with multiple oval, swollen nuclei. Within seven to nine days large, polygonal cells begin to march out from the capillary fragment, and by 30 days they form a monolayer with regions of varying cell density.

In order to identify the cells that are proliferating, we have introduced ^{3}H-thymidine into the medium 12-72 hours after the capillary fragments are plated. This permits the nuclei of cells about to divide to incorporate the labeled nucleotide before the vessel fragments have begun to change their morphology and the ability to identify cell types is lost. Radioautography thus performed has revealed that apparently only mural cells take up the label; we have not seen any recognizably labeled endothelial cells under these conditions. The number of cells which proliferate is small. Only about 1.5% of the mural cells we have counted are labeled, and the rate of growth is slow. Nevertheless, this technique appears to be demonstrating a real difference in the properties of the two types of cells in retinal capillaries, which we think may be studied to great advantage. This tissue culture system for retinal capillaries offers a number of exciting possibilities for study. A variety of conditions and chemical agents can be tested for their effects on cellular growth and differentiation. Biochemical assays can be conducted for enzyme systems that have been implicated in the pathogenesis of diabetic complications, for example aldose

reductase and sorbitol dehydrogenase and the UDPG-hydroxylysine glucosyl- and galactosyltransferases that are involved in the biosynthesis of basement membranes. The growth, development, and biochemistry of retinal capillary cells can be compared with the properties of capillaries from other organs, which can be isolated in a similar manner.

Certain clinical features of diabetic retinopathy suggest questions that need further exploration. Diabetic retinopathy which has a striking predilection for the posterior pole of the eye, is said to be reduced in prevalence in eyes affected with previous central retinal artery occlusion, high myopia, glaucoma or other disorders which produce optic atrophy, and in eyes with extensive destruction of the retina and choroid from inflammatory or other causes. Finally, the "proliferative" form of diabetic retinopathy appears most frequently in juvenile-onset, insulin-dependent diabetics while "background" retinopathy with loss of macular function is primarily a disorder of older individuals. Detailed epidemiologic studies should be initiated to evaluate these clinical observations, most of which (except for the data on high myopia) have been reported in largely anecdotal form. These are important points not only for their prognostic value in clinical practice, but also because they may provide clues to the influence of metabolic processes in the retina as a whole on the development and progression of diabetic retinopathy. One biochemical feature of the retina that has always intrigued me, and that may have importance for the development of diabetic retinopathy, is its tremendous metabolic activity. The retina has the highest rate of anaerobic glycolysis and of oxidative carbohydrate metabolism per unit weight of any tissue in the body. Because of its greater number of neurons, especially in the ganglion cell layer adjacent to the retinal vessels, the macular region should have the highest metabolic activity of any portion of the retina. Does this enormous metabolic capability change with age? What happens to oxygen consumption, glucose utiliza- tion, lactate production, etc., in diabetes and in other abnormal states? It is possible to make fine electrodes to measure pO_2, glucose concentration, pH, and perhaps other items of interest in small regions of the retina in much the same way that retinal electrophysiologists perform in vivo experiments to study electrical potentials in animal eyes. Such experiments might yield useful information.

There has been considerable recent interest in abnormalities of platelet aggregation in diabetics with retinopathy and nephropathy, and also -- accompanied by much controversy -- in the prevalence and importance of capillary basement membrane thickening. Several European workers have claimed that capillary fragility in skin and conjunctiva is increased in diabetics, and that the increase correlates with retinal vascular disease. Since these results have therapeutic implications that could lead to large-scale clinical trials, they should be carefully and thoroughly documented by further laboratory and

clinical studies. I have submitted protocols for the evaluation of
these points which have been approved by the NIH Clinical Review
Committee, but they could and, I believe, should be expanded for use
at other institutions in collaborative efforts that might provide
much more extensive data.

DIABETIC RETINOPATHY

Kenneth H. Gabbay, M.D.

There is considerable evidence to suggest a possible role for increased dissimulation of glucose via the sorbitol pathway in the diabetic state in the mechanism of formation of some diabetic complications. The enzymes of the sorbitol pathway are present in the retina and various other ocular tissues (lens, choroid, iris and optic nerve). Whether this pathway has any involvement in the origin and formation of diabetic retinopathy is still not clear. New techniques for the radio-immunoassay of aldose reductase, and its localization in specific cell types within the retina and other ocular tissues were presented. It was suggested that it might be of importance to know the exact localization of this enzyme within the ocular tissues.

It is clear that at the present time, we do not have any understanding of the normal utilization of glucose by the retina and its vascular components. Because of a lack of the basic knowledge of retinal carbohydrate biochemistry, it is not possible to state with any certainty what are the initial biochemical insults or injuries to the retina in the diabetic state. Since the retina is a complex organ composed of many different cell types (the capillary endothelial and mural cells, the rods and cones and the associated Muller cells, the inner limiting membrane and its role in separating vitreous from the retina, etc.), more knowledge has to be obtained regarding the role and interactions of these different cell types and structures.

Specific Recommendations

1. Tissue and ultrastructural localization of the aldose reductase enzyme within the retina and its associated tissues are strongly recommended.

2. Intensive investigations of glucose metabolism through the various pathways in normal and diabetic retina and associated tissues are needed to further define the abnormality in diabetes.

3. Morphologic and ultrastructural description of certain cell types within the retina (for instance the Muller cell) are required for further understanding of the normal metabolism of the retina.

4. The need for an experimental model for diabetic retinopathy in animals is quite apparent if we are to embark on new approaches to

understanding diabetic retinopathy. In this regard, the human eye
appears to be rather unique in that the changes observed in diabetes
have not yet been adequately reproduced experimentally.

5. Earlier diagnostic tests for retinal disease are necessary to
delineate the earliest changes in the retina. Hopefully such tests
assess changes preceding the development of morphological and structural
changes within the retina and its vascular structure. Such new
directions can be undertaken only in conjunction with and after a
better understanding of retinal metabolism as indicated above. Again,
the need for annual workshops to exchange information and experience
in this field is apparent.

DIABETIC CATARACTS

Jin H. Kinoshita , Ph.D.

Another complication of diabetes involving the eye is cataract. Diabetic cataracts along with galactosemic cataract fall into a class called sugar cataracts. Extensive evidence has accumulated that a common mechanism is responsible for cataracts associated with diabetes and galactosemia. The factor responsible for triggering the process of cataract formation is the enzyme aldose reductase. Under normal conditions the lens aldose reductase does not convert significant amounts of sugar to sugar alcohol. However when either glucose or galactose is present in high concentrations the conversion is substantial in the lens. The formation of polyols within the lens fibers has serious adverse consequence. Because polyols are not rapidly metabolized further, nor are they able to diffuse or leak out of the lens cells or fibers, they accumulate to extremely high levels. This results in a hypertonicity that draws water into the lens and leads to osmotic swelling of considerable magnitude. In essence this is the initial phase of cataract development in diabetes and galactosemia. The other biochemical changes that occur have been shown to be related to the initial osmotic change caused by the accumulation of polyol.

The Ayerst Laboratories have developed inhibitors of aldose reductase. Recently, successful use of these inhibitors has been made to effectively delay the onset of galactosemic cataracts. The earlier experiments involved the injection of the inhibitor into the vitreous cavity. The effectiveness of feeding the aldose reductase inhibitor in delaying the cataract has also been demonstrated. Currently the effectiveness of typical application as a mode of treatment is being studied.

It has been revealed through a series of surveys made that in human adults the maturation of cataracts occurs much sooner in the diabetic than in nondiabetics of the same age group. Thus the adult diabetic stands a greater risk of undergoing a cataract operation than a nondiabetic. The use of an effective aldose reductase may aid in delaying the cataract in these cases.

Research Opportunities

1. Further development of more potent aldose reductase inhibitors.

2. Clinical trials of the aldose reductase inhibitors for treatment of diabetic cataracts.

3. Claims that high prevalence of cataracts associated with diabetes in Pakistan and in the Marshall Islands have been made. It would be helpful to study this population from an epidemiological and biochemical standpoint.

RESUMÉ OF PRESENTATION BEFORE THE
DIABETIC RETINOPATHY WORKSHOP

Arnall Patz, M.D.

The importance of basic research into the problem of diabetic
retinopathy has been stressed by all of the investigators. This presen-
tation concerns basic studies conducted in animal models of proliferative
retinopathy.

In the early 1950s we demonstrated in our laboratory and Ashton's
group in London also showed that oxygen administration to the young
animal leads to an obliteration of the peripheral retinal vascular
complexes. Following removal to room air, just proximal to the
obliterated vascular area (nonperfusing area on fluorescein angiography),
a form of intravitreal neovascularization results after removal to room
air. Indeed, on cross section the intravitreal neovascular tufts are
virtually indistinguishable from the intravitreal neovascularization
that occurs in the proliferative stage of human patients with diabetic
retinopathy. This particular model of retinopathy occurs in virtually
100 percent of the animals treated in this manner, and, indeed, the
localization of the neovascularization can be precisely located by
varying the duration and concentration of oxygen exposure. The intra-
vitreal neovascularization leaks fluorescein in a classic way, exactly
as occurs in proliferative diabetic retinopathy.

Although there is no proof that this form of neovascularization is
the counterpart, or even biochemically the same as occurs in diabetes,
the virtual identical morphology of the two conditions raises the
possibility that indeed the same fundamental mechanism may underlie
both forms of neovascularization. This is particularly intriguing in
view of the neovascularization in the oxygen model occurring adjacent
to the areas of nonperfusion (ischemic retina) and in many patients
with diabetic proliferative retinopathy the neovascularization is
adjacent to, or nearby, the areas of capillary nonperfusion (presumed
ischemia).

In a study of the development of the vascularization in normal
kittens and beagles, Dr. Chung-Ho Chen, a biochemist in my laboratory,
has observed that a soluble vitreal protein is found in linear relation-
ship with the status of vascularization. When retinal vascular activity
is greatest, this protein is highest in concentration and it gradually
disappears from the vitreous once retinal vascularization is complete.
This observation alone might simply be a coincidental one, or indeed
the protein might have simply been present at birth and gradually
dissipate. However, in the oxygen model where retinal ischemia with

nonperfusion is produced, there is a marked increase in this soluble protein suggesting that the original observation is maybe more than coincidental and raising the possibility that this particular protein is in some way related to both processes of normal vascularization and of neovascularization. Bioassays are being developed to test for proliferative activity of this soluble protein and even if this is not the active vasoformative factor it may be a co-factor or associated with the active principle. At least, it may serve as a clue or a marker for the study of basic vasoproliferative factors.

Through the cooperation of Dr. Judah Folkman, we have introduced solid tumors to study tumor angiogenesis factors on retinal neovascularization. Dr. Steven Brem, formerly with Dr. Folkman, is now working in our laboratory on a part-time basis. We have demonstrated that tumor angiogenesis factor (TAF) will stimulate retinal neovascularization. Of even more interest in this particular study is the fact that there may be an inhibitor in the vitreous itself which delays the formation of retinal neovascularization at a much, much slower rate than occurs in other tissues. Conceivably, an inhibitor may be present in the vitreous for neovascularization and a balance of vasoproliferative factors and inhibitor factors may be involved in proliferative diabetic retinopathy.

Brem and Folkman have demonstrated that neonatal cartilage extract inhibits the tumor angiogenesis factor and prevents neovascularization occurring in their models. Since tumors have the ability, based on our own studies, to induce retinal neovascularization, it is very possible that cartilage extract, or some derivative of it, may serve as an inhibitor of retinal neovascularization. Since the extract has been further purified and much less toxic than the original material tested by us, a major study is planned to test this and other possible inhibitors on retinal neovascularization with the hope that a diffusable inhibitor can be developed that will either arrest or suppress neovascularization.

Engerman and co-workers at Wisconsin have observed background retinopathy in alloxan-induced diabetes and we have in a large series of animals with spontaneous diabetes observed background diabetic retinopathy in dogs. However, the proliferative stage of intravitreal neovascularization has never been reported by any investigator and was never noted in our animals. For this reason until a proliferative neovascularization model is found in the diabetic animal, the oxygen intravitreal neovascularization model may prove useful and it is recommended that basic studies be pursued using this model until a proliferative diabetic retinopathy model is obtained.

RECOMMENDATIONS ON MACROANGIOPATHY

Edwin L. Bierman, M.D.

Areas where knowledge is critically needed to provide better approaches to prevention of accelerated atherosclerosis in diabetes.

1. Determination of the effects of:

   a. Genetic diabetes mellitus
   b. Insulin deficiency
   c. Insulin excess
   d. Hyperglycemia

on:

   a. Carbohydrate, lipid, and lipoprotein metabolism of arterial cells:

      1) Endothelial
      2) Smooth muscle

   b. Proliferation of smooth muscle cells

   c. Permeability and viability of endothelial cells

2. Determination of the relation of hyperglycemia and hyperlipidemia to atherosclerosis in different population groups, i.e., Japanese diabetics in rural Japan vs. San Francisco.

3. Determination of the effect of different dietary regimens (reduction of saturated fat and cholesterol and reciprocal relative increase in complex carbohydrates) on:

   a. Metabolic derangements -- glucose, lipids
   b. Progression of atherosclerosis (noninvasive techniques)
   c. Cardiovascular end points in prospective studies

ATHEROSCLEROSIS AND DIABETES MELLITUS: CLINICAL PROBLEMS

Robert Bradley, M.D.

Diabetes mellitus appears to increase greatly the prevalence and rate of progression of atherosclerotic disease in humans. All blood vessels in the body are affected, some more rapidly than others. Greatest morbidity and mortality result from heart disease, stroke, and gangrene. A possible major impact of diabetes upon these principal clinical expressions of macroangiopathy may provide the greatest and most worthwhile challenge to the National Diabetes Commission through coordination of the skills, efforts, and financial support of several or more of the institutes.

At present, little if any evidence exists to support the role of metabolic control of diabetes in preventing or delaying atherosclerotic disease. If the clinical manifestations of macroangiopathy in the diabetic were identical to those found in the nondiabetic, and if the greater amount and more rapidly progressing lesions of the diabetic could certainly be accounted for by the effects of diabetes in elevating circulating blood lipids and arterial blood pressure, it would seem reasonable to continue focus upon a study of the atherosclerotic process per se and not delve into a possible singular role of diabetes as is being done for hyperlipoproteinemia, hypertension, etc. However, highly specific differences between the clinical lesions, apparently produced by macroangiopathy, are found in the diabetic on comparison with the nondiabetic. The highlights are as follows:

A.   The Diabetic Foot. It has been estimated that 85 to 90% of all amputations because of disease occur in the diabetic. Some of these are due to neuropathy and infection causing "wet" gangrene, but by far the greatest problem is that of ischemia produced by occlusion of the smaller arteries below the level of the popliteal, and particularly those of the foot itself. Gangrene is 50 times more common in the diabetic as compared to the nondiabetic male and 70 times more common in the diabetic than nondiabetic female.

B.   Heart. Fatal ischemic heart disease is more common in the diabetic female than diabetic male, particularly striking in younger women, a reversal of the known striking predilection for ischemic heart disease in the male without diabetes. The acute mortality following a myocardial infarction in the diabetic is approximately double that in the nondiabetic, with long-term survival approximately half that of the nondiabetic. Incompletely explained are the cardiomegaly and excessive frequency of congestive heart failure occurring in the diabetic, at times in the absence of major coronary artery disease either by angiograms or

at autopsy. Estimates are that congestive heart failure occurs twice in the male and four to five times in the female with diabetes for each individual without known diabetes. The excess mortality from heart disease in the diabetic appears to be produced by disease of the smaller arteries in the myocardium by a process that may or may not be similar to the microangiopathy identifiable in the eyes and kidneys. A possibility that the poor myocardial function in the diabetic may be related to altered metabolism in the myocardium itself requires further study. Accelerated atherogenesis appearing to occur in the diabetic with renal failure or those on long-term dialysis also remains as an unexplained phenomenon, although the hyperlipidemia associated with these conditions has been invoked as playing a role.

C. <u>Brain</u>. The possibility that smaller cerebral artery involvement in the diabetic accounts for the more recently reported doubled mortality from stroke in the diabetic as compared to the nondiabetic has thus far been poorly studied.

A characteristic role of diabetes in accelerating macroangiopathy is exemplified by the single or combined occurrence of myocardial infarction, stroke, and gangrene in young diabetic individuals, particularly the female and often in the 30's and 40's with normal circulating lipid levels and little or no hypertension. Such may occur on occasion in individuals in their 20's who have manifestations of rapidly progressive microangiopathy, or in those who after 20 to 40 years of diabetes escaping serious trouble with microangiopathy, frequently develop one or more of the larger vessel complications at a relatively early age.

Overall cardiovascular disease accounts for more than three-quarters of the deaths in an identified diabetic population, and heart disease alone causes 54% of all deaths.

The following recommendations represent some of the research into the as yet unexplained features of large vessel disease in the diabetic that may prove fruitful in helping to solve the total problem of ischemic vascular disease:

1. Because of the possible, ill-defined role of diabetes as an independent risk factor in ischemic vascular disease among <u>all</u> individuals, efforts to find a genetic "marker" for diabetes must be intensified.

2. A more definitive morphologic and biochemical study of smaller vessels in the heart, feet, and brain of diabetics may clarify the relationship, if any, between such changes and those found in capillaries, etc., of tissues involved by the characteristic microangiopathic process.

3. The possible role of microangiopathic changes in the vasa vasorum as a source for the original injury to the arterial wall can and should be settled promptly.

4. Suitable models are needed to study the effects of various perturbations upon tissue vasculature, blood vessel response to injury, and upon blood itself, including the role of intravascular elements in producing or repairing injury.

5. At the clinical level improved teaching of foot care for the patient and his or her family is long overdue. Much of the disability, cost, and suffering related to foot lesions is already preventable by the ongoing application of preventive measures.

6. Vastly improved teaching of professionals as to significant versus nonsignificant foot lesions and how to treat them should be a major thrust in any diabetes treatment "center."

7. Improved clinical methods for the earlier detection of vascular lesions and/or effects of treatment upon the tissues involved may lead to discovery of worthwhile interventions, especially if utilized early.

MICROANGIOPATHY AND MACROANGIOPATHY

Godfrey Getz, Ph.D.

1. Any recommendation for further funding of diabetes research should be clearly indicated as an additional resource and should not be provided at the expense of existing programs. Serious consideration might be given to a joint effort between all of the appropriate institutes of the National Institute of Health in building an increased research endeavor in diabetes.

2. As with all categorical endeavors a balance must be preserved between clinical investigation (therapeutic research) and basic research (preventive research). While the former is absolutely necessary, there seems to be no virtue to the budgetary separation of these two central elements of research activity. The balance should be a flexible one capable of being appropriately manipulated by the responsible implementing agencies according to the short-term exigencies of the situation. Were the clinical trials to be separately budgeted through Congress, one can foresee the distinct possibility that the growth of this element might be at the ultimate expense of dispassionate basic research. This opinion notwithstanding, the expense of essential clinical trials and the effect this has on the resources available for basic research support must be continually emphasized before Congress, as undoubtedly it already is.

In implementing new clinical trials with new resources, for example, on the effect of the control of hyperglycemia, on microangiopathy, the investigation should involve a patient population now being treated by physicians indifferent to the importance of "good control" so ensuring that the trial would not involve the denial to participating subjects of therapy they might have received were it not for their participation in an investigative protocol. With the current philosophy of American medicine, it would seem improper to do otherwise, unless the patient population consented to participate after being fully informed of what was at issue including the possible long-term consequences -- a situation which was most unlikely to be realized.

Clinical problems which merit careful patient trials are:

a. The effect of control on the development of angiopathy --
    here capillary basement membrane thickening should constitute
    an important element but not the end point of the
    investigation;

b. The effect of dietary management on the development of
    angiopathy.

3. Basic research should be supported with all available resources. Quality should be the major determinant of support, without specific allocation to particular categorical investigations. However, problems which might be encouraged are:

    a. The search for and characterization of an animal model of microangiopathy, preferably in the nonhuman primate where much work on macroangiopathy is now focused;

    b. The effect of oral hypoglycemics on coronary artery atherosclerosis and myocardial angiopathy;

    c. Pathological investigation of microangiopathy in diabetic hearts (human and animal);

    d. The biology of smooth muscle cells and endothelial cells and their production of extra-cellular protein products. The effect of diet and hormones on these cells and on their interaction with lipoproteins;

    e. Control of lipoprotein synthesis and removal and the influence thereon of hormones and diet;

    f. The effects of hormones and diet on lipid metabolism.

4. The training of diabetologists should receive specific support. However, it seems most important that such training should provide a broad background in applicable basic science and a thorough exposure to the multiple facets of diabetes and its clinical manifestations and problems. This can best be provided within the supported diabetes centers, where these requirements should be met. To assure control over the quality of potential trainees, support should be provided through the post-doctoral fellowships tenable at diabetes centers. A limited number of research career development awards might also be provided from this categorical "money." This mechanism might be unsatisfactory, however, for the training of those interested in the genetics and epidemiology of diabetes, disciplines which may not be well represented within diabetes centers. The pay back provision should be broad, permitting pay back to be worked off in any academic position primarily involved with the handling of diabetes.

5. Even if no additional funds become available or additional programs implemented, a reconvening of this series of workshops in three years to reassess the "state of the art" would be most valuable.

DIABETIC MICROANGIOPATHY

BIOCHEMICAL CONSEQUENCES

Nicholas A. Kefalides, M.D., Ph.D.

I. Introduction

Microangiopathy continues to present a serious complication of
diabetes mellitus and a challenge that requires the efforts of several
investigators in understanding its etiology and control. Characteristic
of the microangiopathic lesion in diabetes is thickening of the capillary
basement membrane and endothelial cell proliferation in various tissues
including the renal glomerulus, muscle, skin, eye and brain.

For several years now, a number of investigators studied extensively
the ultrastructure, chemistry, immunology and biosynthesis of basement
membranes. The ease with which the glomerular basement membrane could
be isolated provided an ample source for the study of this extracellular
matrix. In attempting to characterize more in depth the chemical struc-
ture of glomerular basement membrane, the problem of contamination by
cell debris and interstitial elements became a serious consideration.
This necessitated the study of basement membranes from sources where
extraneous contamination did not present a serious problem; such sources
are the anterior lens capsule of the eye and Descemet's membrane. The
study of basement membranes from a number of tissues helped immensely in
elucidating their partial structure. Thus, the enigma which surrounds
the nature of basement membranes began to unravel slowly as the methods
of approach for their study became more sophisticated and as knowledge
about the nature of structural proteins permitted the formulation of new
concepts regarding protein structure and synthesis.

The knowledge we have acquired and continue to acquire about the
normal state of basement membranes has formed the basis for studies in
naturally occurring human disease and in experimental animal models.

II. Biochemistry of Normal Basement Membranes

In summary, basement membranes are composed of dissimilar protein
subunits. A procollagen-like subunit is associated with noncollagenous
matrix glycoprotein(s). The proportion of the latter components varies
among basement membranes. The various subunits interact via hydrogen
bonds, disulfide bonds and aldehyde-derived cross-links. The extensive
degree of cross-linking renders basement membranes highly insoluble. A
procollagen-like molecule, extracted from calf anterior lens capsule,

exhibits on electron microscopy a filamentous component with a globular portion attached at one end. Treatment of basement membranes with pepsin at low temperature digests the noncollagenous glycoprotein components and allows the collagenous component to come into solution. Purification of the pepsin-solubilized collagen from basement membranes reveals a molecule composed of three identical α-chains. Other unique features include 40-50 residues of hydroxylysine, 128-140 residues of 4-hydroxyproline, 12-15 residues of 3-hydroxyproline, 29 residues of arginine, 35 residues alanine, 2-4 residues of half-cystine, 38 residues of glucosyl-galactosyl-hydroxylysine, 3 residues of mannose, 2 residues of glucosamine, and 0.3 residues of fucose.

Immunochemical studies indicate the presence of three distinct antigenic components and support the evidence that one is collagenous and the other two are noncollagenous glycoproteins. One of the latter corresponds to the nonhelical extension of procollagen. The other is a large-molecular weight highly cross-linked matrix glycoprotein.

Newly synthesized basement membrane collagen is secreted in the extracellular space as the precursor molecule 'procollagen'. The initially synthesized procollagen polypeptide chain has a molecular weight of 155,000 ± 10,000. Pepsin treatment, at low temperatures, of the native triple-helical procollagen-like molecules yields polypeptide chains with a molecular weight of 135,000 ± 10,000. Unlike systems that synthesize interstitial type collagens, the time required for secretion of the newly synthesized molecule is about 60 minutes while for procollagen synthesized by tendon cells the time is 18 minutes. Chemical characterization of the newly synthesized procollagen-like polypeptide chains reveals that 3-hydroxyproline makes up about 11-15% of the total hydroxyproline, that hydroxylysine is glycosylated to an extent of 80-85% and that 95% of the glycosylated hydroxylysine is in the form of glucosyl-galactosyl-hydroxylysine. Usine the parietal yolk sac system, we have shown that the heteropolysac-charide composed of glucosamine, galactose, mannose, fucose and possibly sialic acid is linked to the nonhelical extension of the procollagen-like polypeptide chain via asparigine.

III. Biochemical Studies of Basement Membranes in Diabetes Mellitus

Biochemical studies on the basement membrane in diabetes have centered primarily on compositional analyses and to a lesser extent on biosynthetic studies. The material used for analysis was obtained either from cadaver kidneys of patients who died with diabetes mellitus or from kidneys of animals with experimentally induced diabetes.

Lazarow and Speidel (In "Small Blood Vessel Involvement in Diabetes Mellitus" p. 127, 1964) reported an increase in the total amount of GBM

isolated from kidneys of patients with diabetes but found no significant change in the amino acid or carbohydrate composition. Following this report, Beisswenger and Spiro (Science 168:596, 1970) reported an increase in the hydroxylysine and hexose contents of GBM isolated from patients with long standing diabetes. The authors attributed these changes to increased hydroxylation of lysine and subsequent increased glycosylation of hydroxylysine. On the other hand, Westberg and Michael (Acta Med. Scand. 194:39, 1973) reported that they were unable to confirm the observations of Beisswenger and Spiro of an increased hydroxylation of lysine in GBM from diabetic human kidneys. Shortly after Kefalides (J. Clin. Inves. 53:403, 1974) found no significant changes in the amino acid and carbohydrate composition of GBM from diabetic human kidneys compared to controls. In addition, the collagenous component isolated from the GBM had twice as much hydroxylysine and hexose as whole GBM and the values were similar in both the diabetic and control GBM collagen. In a recent report (personal communication) P. Mahieu, R. Winand and P. LeFevre confirm the findings of Westberg and Michael, and Kefalides.

The changes seen in the amounts of other amino acids not characteristic of the collagen component are difficult to explain. Since disulfide bonds are involved in the cross-linking of the protein molecules in GBM, the observation made by Westberg and Michael and substantiated by Kefalides, that the diabetic GBM contains lower amounts of half-cystine, could be of potential importance. It would require the isolation of the protein component which is rich in half-cystine and demonstrates a decrease in the content of this amino acide in diabetes mellitus. The half-cystine content of the collagen from the control and diabetic GBM was lower than that of the intact basement membrane but did not differ between the two groups. The decrease in sialic acid again is difficult to interpret since GBM preparations are not very "pure" and could very easily be contaminated by protein components having amino acid and carbohydrate compositions different from those of the "normal" GBM. At any rate, it would be difficult to prove with the available data that such changes have resulted from modifications in the protein components of the GBM proper rather than from contamination by cellular or other interstitial proteins.

It would appear that in diabetes mellitus there is not only thickening of the basement membrane proper, but also accumulation of basement membrane-like material in the mesangial region. At present, we do not know the chemical and physical properties of the portion of the basement membrane which accumulates in the mesangium. It is possible that diabetic glomeruli with an excess of basement membrane-like material in the mesangium may yield GBM preparations with less contamination from the epithelial or endothelial cells surrounding the capillary GBM. This may result in preparations of basement membrane with higher amounts of

hydroxyproline and hydroxylysine, amino acids which characterize the collagen component.

There is only one published report dealing with the biosynthesis of GBM in vitro by glomeruli isolated from kidneys of rats with streptozotocin induced diabetes. They studied the incorporation of ^{14}C-proline and ^{14}C-lysine into non-dialyzable protein and concluded that there was increased protein synthesis. Unfortunately, this is an incomplete study.

From all the above studies, we would have to conclude that the cause for the thickening of the GBM in diabetes mellitus is still unknown.

IV. Projections for the Future

The general questions which still remain unanswered and must be answered are: Why is GBM altered morphologically? Is the metabolism of cells that make GBM altered? Why is there proteinuria? What is altered within the BFM proper and how? What is the function of the mesangial cell and how is it altered in disease? What is the chemical nature of the GBM-like matrix in the mesangial region?

a. Ultrastructural Studies. The ultrastructural studies from a number of laboratories have already documented the thickening and other morphologenic changes of GBM in diabetes. Parallel studies have demonstrated an increased number of mesangial cells with marked increase in mesangial matrix. Future studies along these lines should be undertaken only after uniform methods for measuring basement membrane thickness have been established and agreed upon by the laboratories concerned.

b. Epidemiologic Studies. Epidemiologic studies of the kind reported in Lancet, August 14, 1971, pp. 332-334, where a high frequency of diabetes in young adults with congenital rubella has been reported, should be encouraged. Long range studies should attempt to determine the presence of microangiopathy in the absence of clinical diabetes. These type of studies should be helpful in answering questions regarding the pathogenesis of basement membrane changes in diabetes mellitus. Whether these changes precede or follow diabetes mellitus is an unanswered question.

c. Chemical Studies. Compositional studies of whole GBM gave us all the information that one can obtain. Further studies on chemical changes of basement membrane in disease should aim at (1) isolating the three types of glomerular cells, i.e., endothelial, epithelial and mesangial and examining the composition and structure of their plasma membranes, (2) isolating mesangial matrix and studying its amino acid and carbohydrate composition. This may seem untenable at present, but who would have thought 50 years ago that we would learn so much about GBM?

(3) isolating individual protein components from GBM and mesangial matrix that can readily and consistently be characterized by their size, amino acid content, carbohydrate composition and kind and degree of cross-linking.

    d. <u>Biosynthetic Studies</u>. I should like now to recommend an area of research that is likely to yield the most novel and useful information and that is <u>biosynthesis of basement membranes</u>. Glomeruli and cells from glomeruli are capable of synthesizing basement membranes <u>in</u> <u>vitro</u>. This has been also shown to occur in three other systems, namely the embryonic lens capsule, the embryonic parietal yolk sac and the mature Descemet's membrane endothelium. Freshly isolated glomeruli can be used in suspension culture for short-term (4-6 hours) experiments or in organ culture for long-term (1-6 days) experiments. Glomerular cells have been grown in tissue culture. A serious attempt should be made to isolate and grow in culture independently the three glomerular cell types, i.e. the epithelial, endothelial and mesangial.

    The advantages of this approach are the following:

    1. One can follow overall protein synthesis by incubating cells in the presence of radio-labeled amino acids.

    2. The synthesis of a specific basement membrane component, such as its collagen can be followed by the use of ^{14}C- or ^{3}H-proline and its conversion to ^{14}C- or ^{3}H-hydroxyproline. From this type of experiment, information regarding rate of protein synthesis, percent hydroxylation of proline, ratio of 3-hydroxyproline to 4-hydroxyproline, molecular size of the newly synthesized collagen or procollagen, degree of triple-helicity of the secreted collagen, rate of secretion, etc. can be obtained. The use of ^{14}C- or ^{3}H-lysine and its conversion to hydroxylysine can be followed as well as the degree of glycosylation of hydroxylysine and the ratio of the disaccharide to the monosaccharide.

    3. Further useful information can be obtained from studying the sugar incorporation into the noncollagenous peptides of GBM.

    4. Since disulfide linkages are so prominent in basement membranes, one could study cysteine incorporation. We now have a new technique which cleaves peptides at the amino-peptide portion of cysteinyl residues of basement membrane proteins. The peptides one obtains must equal the number of cysteine residues plus one.

    5. Finally, at the organ or cell culture level one can manipulate the environment and study the biosynthetic behavior of cells. The concept of premature senescence of endothelial cells has been proposed and it should be explored.

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V. Needs for Optimal Progress

These studies should be undertaken in clinical centers where patients with diabetes represent an important clinical load. The basic chemical and biosynthetic studies should be undertaken in laboratories that are already carrying out studies on protein and carbohydrate chemistry and metabolism. Development of animal models is very important. There should be no need to create new laboratories, but rather strengthen existing ones.

VI. Patterns for Research

Research support on the chemistry and metabolism of proteins, carbohydrates and lipids with emphasis on the glomerular basement membrane, as well as other basement membranes and the cells which synthesize them should yield fruitful information. Research on lipids assumes importance if we are to study the structure of the plasma membranes and the mode of transport of basement membrane components through the subcellular compartments. I believe research grants and program projects represent the best approach.

VII. Patterns for Training

The studies I have outlined will no doubt be long-term; the need, therefore, to train future investigators in the areas of protein structure and biosynthesis, tissue culture, cell biology and embryology becomes paramount.

RECOMMENDATIONS FOR FUTURE SUPPORT OF INVESTIGATIONS OF DIABETIC NEPHROPATHY

Alfred F. Michael, Jr., M.D.

1. Studies on the role and function of the glomerular mesangium: The nature of mesangial matrix; the effects of the diabetic state on mesangial function; the mechanisms by which the mesangium rids itself of macromolecules (e.g., complexes); the role of mesangial smooth muscle protein (actomyosin).

2. Studies on the extracellular membranes: the mechanisms responsible for increased entrapment of proteins in renal extracellular membranes in diabetes; biochemical alterations in diabetes to define the molecular changes in structure and cross-linkage that correlate with permeability changes.

3. Studies of smooth muscle metabolism in vessels and glomeruli in diabetes.

4. Studies of glomerular cells in tissue culture: identification of cells that make GBM and mesangium in normal and diabetics; studies of the effects of metabolic alteration (e.g., excess glucose, insulin, etc.) on metabolism of these cells.

5. Further studies on the development of appropriate experimental models of diabetes: the changes in GBM and mesangial function; effects of reversal of the diabetic state on the renal, ocular, and systemic vascular lesions.

6. Clinical studies. Establishment of controlled studies in juvenile diabetes -- e.g., ultra-rigid control (thrice daily insulin, weighed diets, etc.) vs. the usually accepted therapy for diabetes. These studies will attempt to evaluate the development of _early_ vascular and glomerular lesions -- muscle capillary measurements, actomyosin distribution in glomeruli, the presence of increased immunofluorescence for serum proteins in these membranes, eyeground alterations, etc. -- in order to evaluate the effect of good metabolic control on the development of these lesions.

The pathogenesis of diabetic nephropathy is unknown. Although not definitively proven, it is likely that the glomerular abnormalities reflect the changes found in basement membranes in other parts of the body, particularly those described in muscle capillaries. Although initial evidence had suggested that the microvascular disease might antedate the development of overt diabetes mellitus, subsequent studies have demonstrated that in most instances changes in basement membrane occur after

the development of the metabolic abnormality. Within the last decade, a number of lines of evidence have suggested that most forms of glomerulonephritis in man are related to antigen-antibody complexes or fixation of antibody to glomerular antigens. At the present time, however, there is no evidence to indicate that immunological mechanisms are primarily responsible for the development of diabetic nephropathy. However, immunopathologic studies of the kidney from patients with diabetes have revealed a number of important findings: (1) Within the glomerular basement membrane a number of different proteins can be identified by immunofluorescent microscopy including immunoglobulins but also nonimmunoproteins such as albumin in an intensity greater than that seen in normal or other diseased tissues. The absence of fixation of insulin or insulin antibody, the inability to demonstrate that immunoglobulins in the serum or those eluted from the kidney fix to kidney structure, and the presence of nonimmunoproteins, suggest that these proteins are deposited in the basement membrane by nonimmune mechanisms. (2) Of interest is the observation that a similar phenomenon is present in tubular basement membranes as well as Bowman's capsule of all diabetic patients -- in contradistinction to findings in normal kidneys or kidneys with other forms of renal disease. The presence of protein such as IgG and albumin in the tubular basement membrane as demonstrated by immunofluorescent microscopy is a highly specific finding, especially in advanced diabetes mellitus and is not seen in other kidney diseases. These changes in glomerular and tubular basement membranes, as well as Bowman's capsule suggests some underlying abnormality of renal extracellular basement membrane in diabetes mellitus that permit entrapment of serum proteins. (3) Recent studies on the antigenic structure of the glomerulus in a variety of disease-states have demonstrated a prominent increase in the quantity and distribution of a smooth muscle protein -- actomyosin -- in the mesangium of the glomeruli of diabetic patients. This is not observed in other kidney diseases. It is of interest that studies by a number of investigators have demonstrated significant expansion of the mesangium in early diabetes mellitus but the relationship of this observation to the changes in the capillary basement membrane have not been defined. There is experimental evidence, however, to indicate a very clear relationship between the glomerular capillary filter and the mesangium: an increase in mesangial uptake of macromolecules in experimental animals has been demonstrated to occur whenever there is increased permeability of the glomerular filter to protein. (4) Experimental studies have also demonstrated that rats with experimentally induced diabetes (streptozotocin or alloxan) develop histological changes in the glomeruli and vessels related to the duration of the disease and that these are associated with the presence of immunoglobulin and complement within the mesangium. Of considerable interest is the observation that these findings can be reversed by correction of the diabetic state -- either by kidney transplantation or by pancreatic islet transplantation.

The exact metabolic alterations that lead to the entrapment of serum proteins in renal extracellular membranes and the increase in actomyosin in the mesangium are unknown. Recent observations have suggested biochemical changes in the glomerular basement membrane in diabetes including a decrease in cystine content which may indicate some alteration in peptide chain cross-linkage. Future studies necessary to define the nature of diabetic nephropathy must include a precise understanding of the role and nature of the glomerular mesangium and its constituent antigens, the factors controlling basement membrane synthesis and the natures of changes in basement membrane that lead to increased entrapment of serum proteins.

LONG-TERM COMPLICATIONS OF DIABETES

Anthony D. Morrison, M.D.

Any discussion of the long-term complications of diabetes mellitus must recognize that what we presently term diabetes mellitus may prove to be a group of diseases with diverse etiologies. By our present diagnostic criteria, all of these disorders would share the ability to induce an abnormality in insulin secretion with a resultant derangement in the regulation of plasma glucose fluctuations. It is possible that certain long-term complications are restricted to specific etiological forms of diabetes; however, from the data presently available, none of the long-term complications appears to be confined to what is presently considered genetically determined diabetes mellitus. It appears reasonable therefore to examine the metabolic abnormalities that are common to all diabetics to determine whether mechanisms exist by which they may contribute to the development of specific long-term complications.

The possibility that hyperglycemia itself may contribute to the pathogenesis of specific long-term complications has not received serious attention in the past, and cannot be dismissed on the basis of the data derived from clinical trials. Without exception, the latter studies have been comparisons of patients with varying degrees of abnormal plasma glucose fluctuations; in addition, their design has given little attention to the role that commonly associated but independently determined genetic abnormalities (such as those affecting lipoprotein metabolism) may play in determining the chemical course.

We have examined the activity of the polyol pathway of glucose metabolism in the inner aortic wall and its role in altering the metabolism of this tissue under in vitro conditions of increased medium glucose concentrations. Using the commonly employed rabbit aortic "intima-media" tissue preparation, flux of glucose through the polyol pathway is increased six to seven fold during a two-hour incubation when medium glucose is increased from five to 50 mM. Under these conditions, there is an increased water content of the tissue associated with a decrease in the insulin space. Based upon speculation that the distance through which diffusion of oxygen and metabolites must occur in aortic tissue approximates the critical diffusion distance for oxygen, the oxygen uptake of inner aortic wall was determined under physiological and elevated medium glucose concentrations. After incubation at 20 or 50 mM medium glucose, oxygen uptake was decreased at a physiological medium pO_2 and could be restored nearly to normal with 95% O_2 or by increasing extracellular osmolality, suggesting that oxygen diffusion becomes limiting for respiration. In addition, elevated glucose concentrations increased tissue lactate production and increased the aortic lactate to pyruvate ratio.

Although these metabolic abnormalities could not be accounted for by increased tissue levels of sorbitol and fructose on an osmotic basis, they do appear to be related to increased polyol pathway activity since they could be prevented by specifically inhibiting the initial enzymatic step in the pathway. Aortic free myoinositol content falls at high medium glucose concentrations and this effect is also prevented by inhibiting the enzyme aldose reductase. The addition of high concentrations of free myoinositol to the medium minimizes the changes in water content and respiration resulting from high glucose concentrations. This effect is not osmotic and polyol pathway activity is unaltered. The adverse effects of increased polyol pathway activity in aorta may thus be mediated, in part, through alterations in the metabolism of myoinositol or of the phosphoinositides.

The above findings are consistent and provide a biochemical basis for altered inner arterial wall metabolism. However, we now have reason to believe that they apply only to the smooth muscle component of the "intima-media." Electron microscopic examination of the freshly prepared inner aortic wall shows marked endothelial cell swelling and/or disruption and this progresses further following a two-hour incubation with preservation of a normal appearing smooth muscle layer. Preparative and incubation conditions have now been altered to permit preservation of a morphologically intact endothelial and smooth muscle cell preparation following a one-hour incubation. This intact preparation exhibits metabolic characteristics very different from those previously reported for inner arterial wall. Thus, glucose uptake is increased but lactate production accounts for only approximately 15% of the glucose uptake and therefore aerobic glycolysis is low. Oxygen uptake is 50% greater than that previously reported and a marked Pasteur effect can be demonstrated with lactate production being 380% greater with anerobiosis. The aortic endothelial cell layer is very sensitive to anoxia with marked morphologic and metabolic changes noted following a ten minute anoxic period and these changes are irreversible. Thus, the metabolism of the composite inner arterial wall and the effects of substrate and various hormonal agents appear to deserve reevaluation.

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THE HEART AND DIABETES

Timothy J. Regan, M.D.

Diabetes mellitus appears to be associated with an increased mortality from cardiac disease (1). This has long been attributed to atherosclerosis of the extramural coronary vessels. However, the relative contribution of coronary artery disease and primary abnormalities of the myocardium has not been established. Although it is generally accepted that there is enhanced atherosclerosis of the aortic-iliac vessels in diabetes, a recent quantitative assessment of the extent of involvement of the coronary arteries indicated that the incidence and severity of coronary disease at autopsy was not substantially greater than in nondiabetic subjects (2). Furthermore, considerable accumulation of glycoprotein staining material may occur in these vessels, both extramural and intramural, without measurable vascular obstruction (3).

The multiple variables that may exist in human adult diabetics makes it difficult to establish a primary disease of the myocardium analogous to that of the kidney. In our initial approach to the question, experimental diabetes was induced in the young adult dog, a species known to have a low incidence of spontaneous arterial disease. A mild stable form of diabetes was produced by using sequential low doses of alloxan (4). After one year, studies of the ventricular end-diastolic pressure-volume relationships were undertaken by volume expansion with saline. The significantly greater rise of end-diastolic pressure in the diabetic dogs compared with that in normal controls supported the interpretation of increased diastolic stiffness of left ventribular muscle in the diabetic group, which was not associated with hypertrophy or abnormalities of cardiac cell structure on electron micrograph. There was, however, accumulation of periodic acid–Schiff positive material in the interstitium, suggesting a basis for the diminished diastolic compliance of the diabetic heart. Chemical analysis of myocardium revealed lipid accumulation in the form of triglyceride and cholesterol. Plasma concentrations of these lipids were not elevated during chronic diabetes, but plasma free fatty acid concentrations were modestly increased.

To determine if human diabetics have evidence of a similar abnormality of myocardium, a group of 25 stable patients without the complications of obesity, hypertension or clinical evidence of heart disease were studied by use of the systolic time interval technique (5). When compared with individuals of the same age, there was a significant increment in the ratio of preejection period to left ventricular ejection time. This did not vary with sex nor was there a variation with duration of diabetes or therapeutic modalities. This abnormality is not as severe as that characteristic of the failing heart and could be

related to a low grade abnormality of myocardial contractility. However, reduced distensibility of the ventricle may constitute the major determinant of this preclinical abnormality, which would be consistent with the animal model described above.

Whether the observed functional abnormality progresses to clinical heart failure may depend on intensification of the underlying pathophysiology in the myocardium or the superimposition of complications such as hypertension, obesity or obstructive disease of the coronary vessels. These latter are not essential for such a course, as suggested by hemodynamic studies of Class I cardiac patients who had established diabetes mellitus without these complications. Patients were accepted for study who had familial diabetes and in whom the diagnosis was established prior to the onset of cardiac symptoms, since glucose intolerance may occur secondary to the onset of a cardiac failure (6). These patients also had no symptoms of classic angina or history of myocardial infarction or valvular heart disease. None were addicted to ethanol and patients were excluded if they smoked as much as one pack of cigarettes per day. Two patients with significant coronary obstructive disease by cineangiography were excluded. The remaining eight were studied at rest, using an indicator dilution technique for measurement of end-diastolic volume and stroke volume. Clinical signs of left ventricular hypertrophy were absent in all but one subject. There was a significant reduction of stroke volume index despite a significant elevation of end-diastolic pressure. While the ejection fraction did not differ significantly from controls, the reduced stroke volume appeared to be secondary to abnormal filling of the ventricles since end-diastolic volume was significantly reduced. Use of a simple index of diastolic wall stiffness, the ratio of end-diastolic filling pressure to volume, indicate a significant increment in the diabetic group.

Although these patients did not show significant coronary arterial disease on angiography and the electrocardiograms were within normal limits, ischemia was not excluded. Atrial pacing was conducted to determine whether a subnormal level of blood flow response occurred during this stress, in view of the alleged small vessel disease that may exist in diabetics. In none of the five subjects so paced was there a decrease in the coefficient extraction of lactate below 20%, calculated from the lactate $\frac{A-V}{A}$ concentrations. This is clearly above levels seen in patients with classic angina, which suggests that the abnormality of myocardial function was not related to ischemia. In addition, electron microscopy was performed on biopsies obtained in two additional diabetics having open heart surgery or mitral stenosis. There was some increase in the number of mitochondria as well as pleomorphism but there was no evidence of swelling. The intercalated disc appeared normal but there was some dilatation of the sarcoplasmic reticulum. Increments in collagen bundles between the muscle fibers were observed.

A more advanced stage of diabetes was studied in 12 diabetic sub-
jects coming to postmortem. Three with significant coronary artery
disease were excluded. The remaining nine included six who died in
heart failure. Heart weights ranged from 300 to 550 grams and three
of the nine had gross scar, approximating one square cm in the free wall
of the left ventricle. On morphological examination there was signif-
icant accumulation of PAS positive material in the interstitium graded
2-3+, analogous to the accumulation seen in the experimental animal
model. In addition, eight of the nine subjects had increased inter-
stitial fibrosis. In its mildest form this was manifest as accumulations
of collagen about the medium to small intramural arteries associated with
normal appearing myofibers on light microscopy. In others, the collagen
fibers penetrated from the periarterial location to lie between muscle
bundles. On trichrome stain, this formed a relatively dense network.
In the three patients with gross scar, this process presumably pro-
gressed resulting in loss of myofibers in a fairly large segment of
tissue. The wall of the smaller intramural vessels was thickened in
six of nine cases. Not all vessels were involved and in none was there
unequivocal luminal narrowing. Consequently no clear evidence of either
large or small coronary vessel occlusive disease existed in these
particular subjects.

To further evaluate the cardiomyopathic features in the diabetic
heart, sections of muscle were taken at postmortem from the free wall at
the apex and base as well as from the anterior and posterior septum.
These were trimmed for gross fat or vascular tissue. The concentration
of triglyceride in four nondiabetic controls was 3.3 uM/g+.7 and in dia-
betics the concentration was 8.1+1.2 uM/g. Cholesterol concentration
in the controls was 4.0+.3 and 5.6+.4 in the diabetics. Phospholipid
concentrations did not differ significantly in the two groups. These
lipid alterations are similar to those in the diabetic animal model and,
as a diffuse process, is consistent with a cardiomyopathy.

Thus it would appear that there are alterations in the myocardium of
many diabetic subjects consistent with a myopathic process. This may be
mild and assume a stable form which may have no clinical significance
to the diabetic in the early stages, characterized by modest accumula-
tion of glycoprotein in the interstium. However, enhanced collagen de-
position in the interstitium, particularly in periarterial sites with
extension through muscle fibers as the disease progresses, may give
rise to heart failure. Since occlusive disease of major coronary arter-
ies presumably occurs at least as frequently as in the rest of the popu-
lation, the preexisting abnormality of myocardium may be a basis for the
enhanced mortality alleged to occur in diabetics during myocardial
infarction.

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AREAS FOR INVESTIGATION

1) Relative role of significant coronary atherosclerosis and cardiomyopathy in producing clinical events.

2) Importance of small vessel disease in determining course of cardiac disease.

3) Neurohumoral and plasma substrate (lipids, glucose) determinants of above pathology.

4) Biochemical studies of myocardial glycoprotein and lipid.

5) Effects of varied dietary and pharmacologic intervention on the cardiac abnormalities, as related to initiation time.

THE ROLE OF PLATELETS AND SMOOTH MUSCLE IN ATHEROSCLEROSIS

Russell Ross, Ph.D., D.D.S.

The concept that the sine qua non of the lesions of atherosclerosis is represented by intimal proliferation of arterial smooth muscle cells that become surrounded by relatively large amounts of connective matrix components associated with both intra and extracellular deposits of lipids has now become quite widely accepted (1, 2). Until the last several years, the principle aspect of these lesions that had received the most attention was the deposition of lipids and the role played by lipids in lesion formation. Although lipid deposition is clearly an important component of lesion formation, it has become quite clear that the role originally envisioned for them is different than the one presently under investigation.

Correlated in vivo and in vitro studies performed in subhuman primates have permitted us to demonstrate the role played by arterial smooth muscle cells in the proliferative response. We have also turned our attention to the importance of the endothelial cell in providing a protective barrier to the artery wall and to the role of the thrombocyte with emphasis upon its participation in the initiation of lesion formation.

The hypothesis that is being examined by John Glomset and me at the University of Washington School of Medicine is as follows: We would suggest that the initiating events that lead to the development of both preatherosclerotic and atherosclerotic lesions is represented by "injury" to the endothelial cells lining the lumen of the affected arteries. Such "injury" may be mechanically induced as would occur in chronic hypertension, as has been demonstrated in a number of laboratories including that of Donald Fry of the National Heart and Lung Institute (3). In this case, very large shearing stresses affect the endothelial cells, resulting in focal sites of desquamation of the endothelium and in altered permeability by the endothelium to plasma constituents. Other types of "injury" may also result in focal loss of endothelium. These would include various forms of chemical "injury," as may occur in chronic sustained hypercholesterolemia, or after various forms of immunological injury, as may occur in graft rejection of an artery, or after induction of serum sickness (4).

Focal desquamation of endothelial cells could lead to adherence and aggregation of platelets at the sites of the exposed subendothelial connective tissue, resulting in the physiological response of aggregation and release of platelet factors (5, 6), which together with plasma components, including lipoproteins, could interact to stimulate smooth

muscle cells to migrate from the media of the artery wall into the intima, and to focally proliferate in these regions of injury. This hypothesis would further suggest that if the injury is a single event then the focal proliferative lesions would be reversible, whereas, if the injury were sustained or chronically repeated, then such chronic injury could lead to a sequence of events that could lead to an irreversible lesion. Secondary factors such as long standing sustained hypercholesterolemia, or other forms of hyperlipoproteinemia could also lead to lipid diposition, both within the cells and in the extracellular matrix surrounding the smooth muscle cells. It is conceivable that these deposits of lipids may play a role in preventing lesion reversibility. Therefore, the hypothesis that we are examining focuses upon two cell types, the endothelium and the smooth muscle cell, and combines the notion of focal endothelial injury, possibly associated with chronic hypercholesterolemia, and arterial smooth muscle cell proliferation as responsible for lesion formation and for the resulting formation of connective tissue and lipid deposition.

To examine this hypothesis we have pursued a series of correlated in vivo-in vitro studies. We have examined the role of mechanical injury and diet in the pigtail monkey (Macaca nemestrina) resulting from the use of an intra-arterial balloon catheter (Fogarty type) and have shown that in normolipemic monkeys, proliferative intimal lesions are formed after focal desquamation resulting from use of the catheter. These lesions take less than six weeks to reach a thickness of 15 or more cell layers within the intima of the artery wall (1, 7). In normocholesterolemic animals the lesions are reversible over a period of six months. In sharp contrast, if the animals are on diets that induce a hypercholesterolemia (250-350 mg%), then the lesions which form appear identical to atherosclerotic lesions in man and become irreversible. The only difference between these two experimental circumstances is the associated hypercholesterolemia in one group of primates, consequently the chronic sustained hypercholesterolemia may be important in these experimental circumstances in preventing the reversibility of the lesions.

To attempt to better understand the factors important in arterial smooth muscle proliferation, we have developed methods in our laboratory for growing these cells in culture and have determined their basic characteristics of growth in culture (8, 9). These studies have demonstrated that, similar to observations in other cell lines and in diploid cells in culture, serum is necessary for their proliferation. A systematic investigation of the importance of serum in cell growth in culture has demonstrated that serum derived from cell free plasma (in which all cells were removed, including thrombocytes) lacked any proliferative capacity (10). When blood platelets were added back to plasma, prior to calcifying the plasma to form serum, all of the proliferative capacity present in whole blood serum, and absent from cell free, plasma derived serum was restored to the latter, by platelets. Further experiments demonstrated that the platelets were specifically responsible for aggregating and releasing the

active factor during the process of exposure of platelets to thrombin during serum formation (10). Thus, the importance of platelet adherence, aggregation, and release has become one of the central issues in the early sequence of events that relate to the stimulation of smooth muscle proliferation not only in vitro but in vivo as well.

In a third series of investigations we have attempted to determine whether or not platelet aggregation and release are important in in vivo lesion formation, together with Dr. Lawrence B. Harker (11).

These studies have an important bearing upon the hypothesis noted earlier, in that after injury to the endothelium and exposure of the subendothelial connective tissue, platelet aggregation and release locally is an important phenomenon that has been observed by many investigators (5, 6). This would suggest that in vivo such injury may occur spontaneously, or at particular focal sites on a recurrent basis, leading to chronic exposure to platelet factors together with plasma lipoproteins. Thus, the interaction of these two components, one derived from the plasma, the other from the platelets, may be important in the genesis of the lesions of atherosclerosis (10).

Finally, the third approach we have taken is to study the role of the platelets in vivo. This can be done in baboons that are made chronically homocystinemic. For some time, homocystinuria has been known to be associated with a marked increase in the level of platelet turnover and with a marked decrease in platelet survival. Such decrease in platelet survival has been commonly associated with platelet aggregation within the vascular system. In animals made chronically homocystinemic by dripinfusion of homocystine at a rate faster than the animal is capable of breaking it down, it is possible to demonstrate a marked decrease in platelet survival. In animals made homocystinemic for at least six days, it is also possible to demonstrate focal desquamation of the lining endothelial cells throughout the arterial tree (11). If the animals are continued on a homocystinemic regimen for six weeks or longer, we were able to observe intimal proliferative lesions of smooth muscle identical to those that we observed following mechanical injury (unpublished observations). These observations would strongly suggest that the platelets are in fact involved in lesion development since the focal desquamation of the endothelium can be shown to be clearly correlated with the marked decrease in platelet survival in these baboons.

Thus, these three experimental approaches, namely studies of mechanical injury, chronic hyperlipemia, and chronic homocystinemia, coupled with the studies in cell culture of the growth promoting properties of platelet factors and low density lipoproteins upon arterial smooth muscle have tended to provide evidence to suggest that platelets and plasma factors play an important role in the genesis of the lesions of atherosclerosis, when associated with focal endothelial injury. Further investigations

from these three points of view need to be correlated with the incidence of disease and with possibilities of reversing or preventing these diseases by interfering in given steps in the process, based upon the knowledge we have gained from these investigations.

CAPILLARY BASEMENT MEMBRANE

Marvin D. Siperstein, M.D., Ph.D.

The following are thoughts regarding the capillary basement membrane aspects of the recent Diabetes Panel. First everyone recognizes, as I repeatedly emphasized, that the quadriceps basement membrane (QCBM) method is a relatively crude one with many methodologic variables. Nonetheless, I think that considering the differences in technique the variation in results has been remarkably small. I suppose the practicality of the procedure as a useful independent marker of diabetes mellitus is best indicated by the fact that Williamson, Bloodworth, Yodaiken, Fisher, and Danowski and now even Steve Fajans and Bob Jackson are all using it to quantify diabetic microangiopathy. I believe that all of the data and, with the exception of Williamson, all investigators have concluded, that there is no relationship between duration of hyperglycemia and QCBM width. This limitation in the procedure is mitigated slightly by the fact that Williamson and our data both show some increase in basement membrane thickening after twenty years of hyperglycemia and Yodaiken, as we heard, is finding a correlation between markedly thickened QCBM and clinically significant vascular disease. The procedure may be more practical in this regard than our group has previously stated.

From the discussion, I think that the most immediate use that the QCBM technique might be put to is finally to determine in a practical, objective study whether tight control of the glucose will prevent the development of basement membrane thickening. The data that Bob Jackson presented, and discussed with me subsequently, certainly confirms the results of our publication earlier this year which indicates that many if not most diabetic children do not have QCBM thickening. Even if one accepts Williamson's assumption that the method will only detect approximately 50 percent of adult diabetics, he still finds very significant QCBM thickening by age twenty. The rather rapid increase in basement membrane width that occurs between ages approximately fourteen and nineteen years should, therefore, readily be detected regardless of the method of fixation or measurement.

I can think of no better situation in which finally to determine whether in fact controlling blood glucose will prevent basement membrane thickening, and I know of no other setting where an answer to this question could be obtained within approximately five years. The method in everyone's hands is easily sensitive enough to detect the order of magnitude of changes that would be expected and, as we discussed, I doubt whether there is a serious moral question if the one versus two dose insulin approach is used. Bob Spiro might well raise the question

that one cannot extrapolate from muscle basement membranes to kidney basement membranes, a point which I have made repeatedly; on the other hand I think there is reasonable evidence to indicate that QCBM thickening is a more sensitive, perhaps too sensitive, indication of diabetic microangiopathy and if one could successfully prevent the lesion in the quadriceps muscle by control of the blood sugar there would be reasonable hope that it could be prevented elsewhere. The alternative, that is BM measurements of a renal biopsy, might well raise serious moral questions to such a study.

Certainly Yodaiken's report that extreme QCBM thickening does correlate with clinical microangiopathy adds a bit of evidence in favor of this approach.

In any case, I believe that an attempt by tight control to prevent the relatively rapid thickening of the QCBM during puberty provides a fairly simple practical way of approaching this question, which I think we would all agree is the most important in diabetology.

MICROANGIOPATHY AND MACROANGIOPATHY: SUMMARY

Robert G. Spiro, M.D.

While the discovery of insulin over half a century ago led to the successful therapy of the acute diabetic syndrome and greatly extended . the useful life of diabetics it has so far not resolved the problem of microangiopathy which now constitutes the most threatening aspect of the disease.

A rational, generally accepted therapeutic or preventive approach to diabetic small blood vessel disease must be rooted in a firm knowledge about the metabolic sequence of events leading to the vascular altera-tions and the role which hormones such as insulin and growth hormone play in their genesis. Indeed the conceptual basis for developing sensitive insulin delivery systems by mechanical devices or islet cell transplanta-tion must ultimately rest on a clear demonstration that this hormone can influence the biochemical steps which lead to capillary disease in the diabetic.

The foundation to a rational approach to an understanding of diabetic microangiopathy was laid about fifteen years ago when electron micro-scopic studies revealed that the capillary disease of the renal glomer-ulus is characterized primarily by thickening of the basement membrane. Further studies indicated that the basement membrane thickening is usu-ally accompanied by an accumulation of similar material in the mesangium and that the beginning of both processes appears to coincide with the onset of metabolic disturbances of diabetes and to progress with the duration of the disease.

These morphological studies indicated that an understanding of the biochemical basis of diabetic capillary disease would depend to a large measure on knowledge pertaining to the chemical structure as well as to the biosynthesis and degradation of the basement membrane. In my labora-tory this biochemical approach has already provided some basic under-standing of the structure and metabolism of the basement membrane and its alteration in human and experimental diabetes. The major contributions which we have made in this area may be summarized as follows.

1. A procedure has been developed for isolating glomerular basement membrane from various species including man in a high degree of purity.

2. The membrane has been shown to consist of glycoproteins belonging to the collagen family.

3. The chemical structure of two distinct carbohydrate units (a disaccharide linked to hydroxylysine and a heteropolysaccharide attached to asparagine) has been elucidated.

4. Solubilization of the membrane by cleavage of disulfinde bonds (which form the major peptide cross-links) has been achieved.

5. The solubilized membrane has been resolved into its numerous glycoprotein subunits by gel filtration, ion exchange chromatography and preparative polyacrylamide gel electrophoresis.

6. A small glycopeptide containing both types of carbohydrate units on the same peptide chain has been isolated from proteolytic digests of the membrane.

7. The kidney glucosyltransferase and galactosyltransferase responsible for the assembly of the hydroxylysine-linked disaccharide unit have been purified and very extensively characterized.

8. In vivo studies in the rat with radiolabelled amino acid precursors have shown that the turnover of the glomerular basement membrane is exceedingly slow (comparable to insoluble collagens).

9. In alloxan diabetic rats the level of the kidney glucosyltransferase involved in basement membrane synthesis was found to be markedly elevated but could be restored to normal by early and careful insulin treatment.

10. A distinct chemical alteration was observed in the composition of glomerular basement membranes isolated from human kidneys with advanced diabetic glomerulopathy. The most pronounced aspect of this abnormality was the occurrence of increased hydroxylysine and hydroxylysine-linked disaccharide units.

11. Methodology and concepts relating to the structure and biosynthesis of glycoproteins in general have been developed in parallel studies on other tissues and other proteins.

Future research relating to the biochemical basis of diabetic microangiopathy might follow some of the following lines.

1. The compositional differences observed in the diabetic glomerular basement membrane must be explained in terms of subunit alterations.

2. The subunit structure of the membrane must be further defined to permit an understanding of its filtration function in molecular terms.

3. An _in_ _vitro_ system must be developed in which glomerular basement membrane assembly can be studied in detail and hormonal influences, particularly those of insulin and growth hormone, can be evaluated.

4. The glomerular cell primarily responsible for basement membrane synthesis must be identified and its general metabolism in diabetes must be studied. An attempt should be made to grow this cell in tissue culture and hormone receptors on its surface must be identified.

5. The physiological degradation of the basement membrane must be studied in order to account for the polydispersity of its subunits.

6. A continued search for experimental diabetic animals which develop glomerular disease must be made.

7. The turnover of basement membrane subunits in diabetes must be closely studied and the influence of insulin, growth hormone and glucose levels on this process must be evaluated.

These ambitious biochemical investigations can only be undertaken if funds earmarked for diabetic research become available. Furthermore one would hope that additional funds would be designated for the training of young investigators competent to carry out these studies on the biochemical basis of diabetic microangiopathy.

MICROANGIOPATHY AND MACROANGIOPATHY IN DIABETUS MELLITUS

Daniel Steinberg, M.D., Ph.D.

It is generally accepted that atherosclerosis and its complications strikes prematurely in the diabetic and that there is excess mortality in the diabetic. As Dr. Bierman nicely pointed out, there are multiple known risk factors relating to atherosclerosis that occur with a higher frequency in the diabetic population. Thus, the diabetes-atherosclerosis interaction is complex. Whether or not the sum of the contributions made by know risk factors (hypertriglyceridemia, hypercholesterolemia, hypertension, obesity) account adequately for the excess morbidity and mortality is not certain but there is some suggestive evidence that there is a residual excess risk. This might be attributable to microangiopathy or to hyperglycemia (directly or indirectly) or to some underlying metabolic defect common to the pathogenesis of both diabetes mellitus and atherosclerosis.

The areas of investigation that seem promising include:

1. The involvement of vasa vasorum in microangiopathy. This is perhaps the most obvious way in which the two diseases might be related.

2. The effects of glucose, ketone bodies, and other metabolites abnormal in diabetes on the metabolism of arterial wall and smooth muscle cells in culture.

3. Clinical studies of lipoprotein turnover in diabetes to ascertain whether there are any systematic deviations in overall lipoprotein metabolism.

4. Studies of the effects of hyperglycemia per se on arterial wall metabolism. (This is a possibility but the preliminary data that we heard really doesn't look very strong, at least with regard to the importance of the polyol pathway.)

There are, of course, many other research avenues to be explored. At this state of the art, however, it is difficult to select intelligently. Perhaps more basic work needs to be done in the two diseases separately before a concerted attack can be made on their interaction. At the same time, the awareness of diabetes as a perturbed state that alters the course of atherosclerosis will undoubtedly lead investigators interested in the latter to explore specific aspects such as the effects of insulin as they explore the pathogenesis of atherosclerosis.

It would probably be premature to launch any massive program in "diabetes-atherosclerosis." However, the Institutes involved should surely be on the alert to support and encourage investigators trying to capitalize on the chance of learning more about both diseases by studying their interaction.

RECOMMENDATION FOR ULTRASTRUCTURAL STUDIES OF DIABETIC CAPILLARY BASEMENT MEMBRANE DISEASE

Joseph R. Williamson, M.D.

Recent quantitative ultrastructural studies of capillary basement membrane disease in diabetes in our laboratory and in the laboratories of several other investigators provide strong evidence in support of the following conclusions.

1. There is a positive association between the duration of insulin deficiency and the development and progression of capillary basement membrane disease in those diabetics in whom the onset of diabetes can be accurately dated, i.e., juvenile onset diabetics.

2. A number of factors not directly related to insulin deficiency, e.g., venous pressure, age, sex, and a puberty-related permissive factor(s), markedly influence the accumulation of capillary basement membrane in diabetics as well as in nondiabetics.

3. Basement membrane thickening tends to be segmental in character which suggests that local or regional factors may be important in the pathogenesis of basement membrane thickening.

4. We find no evidence for the existence of any genetic determinant of vascular disease operating in concert with or independent of the insulin deficient state. (The only investigator reporting a significant prevalence of basement membrane disease in prediabetics is Siperstein.)

The important implications of these findings regarding the direction of future research on diabetic vascular disease are: (1) diabetic vascular disease is in some way the consequence of insulin deficiency rather than of some unique genetically determined perturbation in basement membrane synthesis or degradation, and (2) the pathogenesis of diabetic vascular disease is multifactorial.

On the basis of these observations and conclusions, I would recommend that investigations in the following three areas be pursued with vigor.

1. Studies should be undertaken to identify specific pathophysiological variables which influence basement membrane accumulation in diabetic and nondiabetic humans and experimental animals. In addition, further studies are needed to elucidate the mechanism(s) whereby the effects of insulin deficiency and other pathophysiological variables on basement membrane accumulation are mediated.

2. The possibility that insulin replacement therapy by the best methods available, i.e., two to three daily injections of mixed insulin together with appropriate dietary measures, might significantly decrease or delay the onset and/or progression of diabetic vascular disease (large and small) should be examined in new or recently diagnosed juvenile onset diabetics. The need for such a study is urgent because of the implications of its outcome on therapeutic goals and the management of diabetics. The vast majority of insulin requiring diabetics are receiving only a single daily injection of insulin and are almost certainly not controlled nearly as well as they could be by using divided doses of mixed insulins. If it were clearly documented that better control could be readily achieved by the latter regimen, as claimed by its advocates, and that it did prevent or significantly delay development or progression of vascular disease, the study would have a tremendous impact on the treatment of diabetes and on morbidity and premature deaths due to vascular disease.

3. It is my belief that the greatest handicap to elucidation of the pathogenesis of diabetic vascular disease, large and small, is the lack of suitable laboratory animal models. In regard to small vessel disease, with the possible exception of the dog, diabetic retinopathy and nephropathy unequivocally comparable to that occurring in man have not been described in experimental animals. Unfortunately, the length of time required to produce these lesions in dogs and the cost involved seriously limit the usefulness of the dog as a laboratory model of diabetic vascular disease.

The failure to detect diabetic vascular disease in laboratory animals comparable to that in man may be due to species differences in secondary metabolic perturbations and hormonal imbalances associated with insulin deficiency, to species differencies in dietary and nutritional requirements, etc. Since in many instances the presence of diabetes in laboratory animals is found incidentally by investigators who do not have facilities available to assess vascular disease, a central laboratory to which such animals or their tissues could be sent for complete morphological studies including quantitative capillary basement membrane studies, could be of great assistance in developing appropriate laboratory animal models of diabetic vascular disease. Such a facility could and perhaps should be an existing laboratory already engaged in or experienced with quantitative electron microscopic basement membrane studies. The director of such a facility as well as NIH and other agencies concerned with diabetes research would need to make a special effort to publicize the existence of the facility and encourage investigators of all nations to cooperate in making diabetic animals of all species available for study.

DIABETIC MICROANGIOPATHY AND MACROANGIOPATHY

Ralph E. Yodaiken, M.D.

Ways and means of applying our expertise to new problems will be discussed under four main sub-headings:

1. Evaluating the extent of capillary involvement.

2. The relationship between microangiopathy and macroangiopathy.

3. Environmental factors relevant to diabetic capillary pathology.

4. A proposal to establish a center for the study of vascular disease in diabetes.

1. The Extent of Capillary Involvement

It is not known whether the lesion described in peripheral capillaries of diabetic patients (1,2,3) is limited to diabetes or not. Possibly a similar progression of events gives rise to basal lamina thickening (BLT) in other chronic diseases. Furthermore, since careful quantitation of capillary lesions is lacking in studies on tissue other than skin muscle and kidney, the extent of capillary involvement in diabetes is uncertain and this needs to be corrected. To illustrate this point -- what is the relationship between diabetic capillaropathy and cardiac pathology in diabetes? Cardiovascular death is the commonest cause of death among maturity onset, or Type II, diabetics in this country (4), and a high proportion of patients who die as a consequence of myocardial infarction have no demonstrable occlusion of the coronary arteries, the myocardial necrosis being the primary event (5,6). In a recent study on Israeli diabetics (7), a positive correlation between thickening of the basal lamina and low capillary pressure was noted. Confirmation of this observation will strongly suggest, therefore, that ischemic changes of the myocardium and/or myocardial infarction in some diabetic patients is the consequence of two factors, small vessel disease and coronary artery atherosclerosis, both of which combine to produce tissue necrosis and initiate thrombosis. A similar pathogenetic pathway may exist in peripheral tissues where gangrene of the toe may occur without occlusion of a major vessel.

The problem needs to be investigated by two methods: (1) correlating capillary pressure with basal lamina thickening where it is found, and (2) establishing a baseline morphometric analysis of cardiac capillaries. The first is being carried out at present with our patients in Jerusalem.

Other studies need to be initiated. For the second method, it should not be difficult to obtain fresh specimens from cardiac surgery patients and begin a systematic study of the capillaries of the myocardium. In addition, autopsy material can be used in a manner to be described below. Routine autopsy specimens are not suitable for study of tissue at an ultra structural level. The "instant autopsies" being carried out at the University of Maryland School of Medicine in Baltimore offers a suitable source of tissue (8). This source would provide the heart for analysis and quantitation, as well as other organs, such as the pancreas and the brain, for which baseline data is needed.

In summary: (1) The exact extent of the capillary lesion needs to be determined. (2) It is essential to know if the lesion occurs in other diseases. (3) A baseline for morphometric evaluation of capillary pathology in all tissue is required.

2. The Relationship Between Microangiopathy and Macroangiopathy

A number of investigators have come to the conclusion that diabetic capillary pathology is a different disease entity to large vessel or macroangiopathy. One of the observations requiring cautious evaluation at this time is the apparent clinical absence of diabetes (9) and of small vessel disease (10) among populations such as Asiatics. The question that needs to be answered is whether this is an absolute or a relative absence of capillary pathology due to lack of adequate means of investigation. Or if, like atherosclerosis, capillary disease is diet dependent. My experience and that of others (11) suggests that in those populations which do not exhibit significant atherosclerosis, the prevalence of small vessel disease as evidence by retinopathy and nephropathy is similar to that of most other diabetic populations. Assuming this is to be the case, then there is a tendency to believe we are dealing with two different pathologies, one affecting capillaries, the other affecting muscular arteries. However, is this so? If it is confirmed that capillaropathy is widespread and characteristic of diabetes, then the vasovasorum should also be involved. The sensitive inner third of the media of large vessels may be deprived of adequate nutrition or oxygen leading to degenerative changes in that region. If a deleterious diet produces an additional insult to large vessels thus compromised, severe atheroma may result. In other words, among diabetics early atherosclerosis may be the consequence of capillary pathology (vasovasorum), as well as dietary factors. This would account for the fact that small vessel disease is common to most diabetics, but atherosclerosis is a major cause of morbidity and mortality only among diabetics in affluent countries or eating refined diets.

In summary: The hypothesis is that in diabetes, small vessel disease may be contributing to tissue necrosis in a number of situations and that where dietary factors are also important atheroma, gangrene, or infarction are common and severe. This aspect of capillaropathy needs to be investigated.

3. Environmental Factors

These have been virtually ignored up to the present. Obvious environmental factors of which cognizance should be taken are smoking, diet, and oral contraceptives, all of which are known to compromise the vascular tree at various levels. One group of environmental agents, which may be profitably examined, is trace metals. There is some evidence that cadmium (12), copper (13), and chromium (14) play roles either in vascular disease or in the pathogenesis of atherosclerosis. Do trace metals affect peripheral capillaries? Since lead is ubiquitous in our every day environment and since the content of lead in our tissues is so much more than that in the tissues of people living in other countries (15), it would be appropriate to determine what role lead and other trace metals play in vascular pathology at the ultra structural, microscopic, and macroscopic levels. Zinc deficiency for example appears to be essential to new capillary formation and the maintenance of capillary status (16). It should be borne in mind also that a balance may exist between one trace metal, say copper, and another, say iron (17), an increase in one leading to a decrease in another. Furthermore, it is quite clear that trace metals cross the placental barrier and appear in the tissues of newborn infants. The effects of trace metals and trace metal deficiencies on the capillaries of diabetics could be easily explored by correlative studies on capillaries, muscle tissue, blood, and hair samples.

In summary: (1) The effect of environmental factors on vascular disease needs to be evaluated. (2) Because lead is ubiquitous and because a balance exists between one trace metal and another, the effects of trace metals on the vascular tree must be determined. (3) Since trace metals cross the placental barrier, they may play a role in the "genetics" of diabetes. This needs to be investigated.

4. A Center for the Study of the Vascular Complications in Diabetes Mellitus

From all of the above, it seems reasonable to suggest that a center be established to coordinate all the studies of micro and macroangiopathy in diabetes. This does not mean that other laboratories should be closed or that other areas of investigation not be funded. On the contrary, the greater the diversity of interest and attack on the

problem, the more likely we are to achieve our goal. However, a center would be most helpful in coordinating research projects and evaluating results. Such a center might provide facilities lacking elsewhere, such as adequate means of data collection and analysis. It may also be possible to investigate problems which are not directly related to diabetes. For example, what is the relationship between carcinoma and diabetes mellitus? It has been suggested that thickening of the basal lamina may be an important factor in the tendency for diabetics to develop infections because the thick wall provides a barrier to the passage of white cells from the vascular compartment to the affected area (18,19). Is this true for malignant cells as well? It is possible that among diabetics who have thick capillary walls the dissemination of malignant neoplasms does not occur or is less likely to occur than in diabetics with thin-walled capillaries.

From such a center, cohort or prospective studies could be launched to investigate capillary pathology among diabetic families in small communities. The capillaries could be monitored over a period of five to ten years along the lines of the Framingham Study. The families of nondiabetic spouses would be suitable controls and an annual cardio-vascular workup offered as an inducement to participation in the study. Tissue processing and data analyses would be carried out at the center.

Finally, a center for the study of vascular disease among diabetics would provide much needed training and education for graduates and under-graduates and ultimately increase the number of investigators and assistants in this field. This is extremely important because the under-standing of diabetes and the progression of vascular disease is poor among the general population of medical practitioners. While regimenta-tion in training or teaching runs counter to our philosophy, steps need to be taken to ensure that as many physicians as possible learn about the pathogenesis of diabetic vascular disease, the factors which promote exacerbations, and the best known therapeutic measures to combat progression of these complications. One of the best precedents for the establishment of a center is perhaps the Joslin Clinic. For years it was recognized that the Joslin Clinic was the center for the study of diabetes. Whatever came out of the clinic was avidly read, discussed, and practiced, both domestically and overseas. If one wanted to learn about diabetes -- Boston was the place to go. Now many excellent centers exist throughout the country, but much of the ground-work was laid in Boston.

The idea of a center for the study of vascular disease in diabetes is to lay the groundwork for this aspect of diabetes -- provide a place to which physicians can gravitate for refresher courses or for training in the subject, where workshops are a weekly occurrence and both domestic and overseas discussants are invited to participate throughout

the year. In this way the best investigative and therapeutic methods can be continually reported and evaluated and the stimulus generated will be widely disseminated.

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Patients with neoplasia

Relationship between capillaropathy and neoplasia.

↓ Biopsy Specimens

Large Vessel Disease

Cardiac Surgery Patients

Data for Analysis ← → Biopsy Specimens

Animal Studies

Diabetic patients other than prospective studies. "I have a young diabetic who is developing diabetes. Could I have an assessment of his capillary status?"

↓ Biopsy Specimens

CENTER

Training for Physicians and Pathologists in examining and evaluating vascular disease in diabetes.

| Epidemiology | EKG Evaluation | X-ray Evaluation | Tissue Lab |
| Field Training Med/ParaMed personnel | Blood flow studies | Surgical techniques | Training of Technicians |

On-going "workshops"—invited speakers from all parts of this country and overseas to provide stimulus and updating of methodology.

Cohort or Prospective Studies

North   East   South   West
Small communities selected on geographic and demographic basis

Data for Analysis

Biopsy Specimens

Field Workers

Instant autopsies

Specimens processed at lab

Data for Analysis

Trace Metal Laboratory

Data for Analysis

Trace Metal Investigator

Biopsy Specimens

CONTRACEPTION IN THE DIABETIC WOMAN

Ronald A. Chez, M.D.

The most effective reversible method of contraception at the present time is the combination pill.

Carbohydrate metabolism is one of the most widely studied fields in women using oral contraceptives. There is a general impression derived from all the reports that a few women do have a marked deterioration of carbohydrate metabolism while using the pill, and that most women have a mild elevation of blood glucose while taking the pill. The frequency rates with which these problems occur are a direct function of rigor of the test of glucose tolerance applied.

Although the literature in this area is voluminous and continues to grow, there is difficulty in comparing studies one to the other. Some experimental designs are prospective, some are retrospective, and some are cross-sectional. Few have adequate controls. The testing procedure frequently varies in complexity. The drugs under investigation are both sequential and combination. The individual component drugs are varied, the drugs have been used for various lengths of time, and the drugs are present in a variety of doses. The subjects taking the drugs vary in important characteristics such as family history of diabetes, age, weight, and parity.

When considering the possibility that oral contraceptives may produce permanent diabetes mellitus in otherwise normal women, the factor of advancing age must be considered in any long-term perspective study in patients taking the pill. It must be eliminated as a factor from the magnitude of any increase.

Most studies suggest that the minor alterations in carbohydrate metabolism associated with the pill are reversible within three months after stopping the drugs.

I cannot be in agreement with the belief that gestational diabetes is a contraindication to the prescription of the pill. First, the definition of gestational diabetes is often slovenly and has not been applied with any rigor. Second, there is no information that permits us to say with accuracy the incidence of converters is increased by the use of the oral contraceptive agents. Third, the patient with diabetes mellitus can receive the pill and in most cases the management of her clinical state will not be adversely affected. Fourth, the prescription of the pill in all patients is one that requires and demands frequent monitoring. The last reason is that the alternative methods of contraception are frequently associated with the need of abortion as a backup,

permanent methods of sterilization, or mechanical methods that may
be unacceptable because of social, educational, moral, or religious
reasons.

I prefer to individualize the care of these patients and to allow
them in an informed and active way to participate in their care.

MODEL -- DIABETES MELLITUS PREGNANCY

Ronald A. Chez, M.D.

Despite the wealth of information from the work of investigators, human pregnancy complicated by diabetes mellitus remains a frequently life-threatening disorder for the fetus and less commonly for the mother. Although there can be little argument with the oft quoted Pope thesis, "The proper study of mankind is man," it is apparent that animal models must play a crucial role if we are to understand not only the pathogenesis of problems in pregnancy, but therapeutic approaches as well. This concept becomes particularly true when questions that relate specifically to the fetus must be asked. The limitations to access to the human fetus are considerable from ethical and political constraints.

The presence of diabetes mellitus in animals has been reported in a variety of species, but the incidence is not easily defined. Spontaneous hyperglycemic syndromes infrequently occur in animals that lend themselves readily to breeding in the laboratory. Although there are important lessons to learn from those animals with spontaneously occurring syndromes, it is necessary to create animal models. Hyperglycemic states have been established in animals via pancreatectomy, electrolytic lesions in the hypothalamus, and the use of drugs such as alloxan and streptozotocin. Each has its advantages and disadvantages. With regard to species selection for valid extrapolation to the human there can be considerable question about the usual laboratory animals because of length of gestation, litter size, and basic diet of the mother.

We have centered on the Macaca mulatta, Rhesus monkey, as our model and have induced hyperglycemia with the drug streptozotocin. The monkey has particular appeal as a model for humans because in many respects its pregnancy equates to that of the human. The placentas are extremely similar both on light and electron microscopy, and there is a single gestation with the length of gestation about five and one-half months. The newborn's functional maturity equates to that seen in the human. Physiological changes in the mother during pregnancy are equivalent both from a cardiovascular, renal, respiratory, and hemologic point of view and particularly in the area of carbohydrate metabolism. Although there can be problems with regard to availability, cost, and handling, the monkey does lend itself to a limited degree of fetal experiments when done under an acute situation. Of particular value is the fact that it is possible to sequentially obtain monkey fetal blood without interrupting the integrity of the amniotic cavity nor jeopardizing the blood supply to the placenta.

Since glucose occupies a central role in energy requirements for the fetus, it is possible to speculate that hormonal controls to insure and facilitate plasma glucose homeostasis must be operative in the fetus. This is not the case in the normal primate pregnancy. Specifically, fetal plasma glucose is a direct function of maternal plasma glucose. The concentration gradient between the two pools serves as the driving force with the mechanism most likely facilitated diffusion. The hormones that are involved with carbohydrate metabolism such as insulin, glucagon growth hormone, and placental lactogen do not cross the placenta in either direction from mother to fetus or fetus to mother.

Although insulin is present in the fetal pancreatic beta cell, the insulinogenic stimuli of hyperglycemia and hyperalanemia are not associated with insulin release. Fetal plasma insulin increments are found with the combination of theophylline in glucose or infusion of dibutyryl cyclic AMP. This suggests that the synthesis of insulin is operative in the fetus but that the releasing mechanisms are not operative either because of an excess of phosphodiesterase activity or inadequate cyclic AMP production.

Similarly, when fetal alpha cell function is examined in the fetus glucagonogenic stimuli of arginine and hypoglycemia do not result in changes in fetal plasma glucagon. An infusion of L-Dopa to the fetus does result in glucagon release. Therefore, glucagon is also present in the fetal pancreas and can be released given the proper stimulus.

The administration of streptozotocin to the monkey results in a hyperglycemic syndrome which is characterized by polyphagia, polydypsia, polyuria, and weight loss. Pregnancy is associated with fetal macrosomia, placental hyperplasia, polyhydramnios, and interuterine death in the third trimester. Therefore, the clinical syndrome equates to that which is seen in human pregnancy complicated by diabetes mellitus. When the fetus of a streptozotocin mother is stimulated by a single bolus injection of glucose, there is prompt insulin release from the pancreas. There is also fetal hyperinsulinemia and fetal beta cell hyperplasia.

Many of the observations that have been obtained from the Macaca mulatta have been substantiated or confirmed or originally found in human pregnancy. Therefore, there is support of the belief that an animal model of carbohydrate metabolism in normal and glucose intolerant human pregnancy does exist. Perspective is of course required. Diabetes mellitus is not just glucose intolerance. Biologically, the Rhesus monkey is as heterogeneous in its stock as man. Practically there are important considerations from a laboratory scientific support point of view. Perhaps the most important consideration is the fact that the experiments are performed on fasted animals in an acute anesthetized surgical preparation. The ability to utilize a chronic model such as is available in the sheep has not yet been obtained.

The basis of these studies allows the conjecture that therapeutic approaches can be tried in the animal model and then extrapolated to human. Further, the presence of fetal macrosomia secondary to hyperglycemia and fetal hyperinsulinemia may provide a clue to the management and care of patients with intrauterine growth retardation.

INFANTS OF DIABETIC MOTHERS

Marvin Cornblath, M.D.

It has become apparent that through advanced obstetrical monitoring techniques as well as sophisticated methods for support and maintenance in intensive care nurseries, that the perinatal mortality and morbidity of infants of insulin dependent and gestational diabetic mothers has continued to decrease over the past decade. Currently, the risk of mortality in the perinatal period is essentially two to three times that of the nondiabetic mother and the majority of the mortality is related to congenital anomalies. A number of risk factors can be identified that put the infant at greater jeopardy. It should be emphasized that the goal of a diabetic pregnancy is an infant who develops to his optimum abilities and not merely a live-born infant who survives the neonatal period. The maternal risk factors are listed on Table 1 and those that require emphasis in the future, obviously are related to improving metabolic control either by early education or early hospitalization of all high risk mothers as well as the prevention of clinical pylonephritis and reaching the "neglectors" in order that they take advantage of available medical resources. The risk factors in pregnancy are also amenable to therapy especially toxemia and careful monitoring of placental insufficiency, fetal distress, and fetal maturity. By increasing gestation by one week it has been possible to significantly reduce the major killer of infants of diabetic mothers i.e., hyaline membrane disease. However, this is a naive simplification since the excellence in resuscitation and maintaining respirations in modern newborn intensive care nurseries, while paying meticulous attention to environmental and metabolic needs has reduced mortality due to hyaline membrane disease to minimal figures.

Another important point is that many infants of diabetic mothers and especially gestational diabetic mothers, have an uneventful course. One of the major needs of future investigation and research is to better define the gestational class A or any class diabetic who is pregnant and presents a risk to her fetus. Screening by blood glucose or oral glucose tolerances is a very coarse screen and it is obvious that more precise measure of defining those women who are actually at risk to have a morbid infant are necessary. These may well be related to the sophisticated assay of other hormones or hormone metabolite interrelationships or ratios. This should be a major and significant area of research in the future.

The multiple problems in the IDM and IGDM were outlined (Table 2). Evidence is presented that there is hyperinsulinemia in these infants but again individual variations were emphasized. It cannot be overemphasized that often the individual patient is so important to avoid

destructive generalizations. An example of this are the successful pregnancies reported by Dr. Younger in patients with retinitis proliferans whose retinal changes improved with pregnancy. Previously, generalizations would have demanded that these pregnancies be terminated on clinical grounds alone.

The importance of multiple parameters of measuring metabolic homeostasis including assays of glycerol, glucose, free fatty acids, ketone bodies were emphasized in the presentation. A hypothesis for the pathogenesis of hypocalcemia was discussed. No definitive conclusions are justified.

A high frequency of heart failure (17%) was reported in 42 consecutive infants of diabetic mothers from the Cook County Hospital. None of these infants had hyaline membrane disease and the mean period of gestation was 38 weeks. The question was raised whether we are now substituting heart failure as a problem in place of hyaline membrane disease with prolonged gestation. No etiology or pathogenesis was apparent in these infants except a number were anoxic and asphyxiated at birth and a significant number had hypoglycemia and hypocalcemia. A theoretical basis for the pathogenesis of heart failure was presented, related to the unique changes in electrolytes and viscosity of the diabetic coupled with both asphyxia and Cesarean section. Although theoretical, this theory is subject to experimental verification and again indicates an area of importance to be investigated.

A summary of the multiple metabolic and hormonal adaptations that occur in the neonate and the multiple measurements that are necessary were discussed. These are briefly summarized in the table headed "Infants of Diabetic Mothers" indicating the interaction between environmental factors, metabolic fuels and hormones (Figure 1).

In conclusion results in my own nursery between 1966 and 1968 were compared with the results in 1971-73. It was emphasized that it is critical to compare recent events with those in the not too distant past. Data from the early 60's and late 60's are irrelevant when one considers the types of care and measurements and support provided in intensive care nurseries today. It is most critical to have an ongoing collaborative analysis of problems related to infants of diabetic mothers if any current recommendations are to be made.

In summary, major areas of needs (Table 3) were clearly identified involving studies of metabolic and physiological parameters in the fetus and perinatal period. What is optimal adaptation and intervention for the newborn infant and certainly what are the emotional-behavioral as well as metabolic and environmental factors that will provide the optimal environment for the neonate? The need for long-term data on what the

outcome of infants of diabetic mothers was emphasized. Again, prevention of problems is most critical and more data are needed in this area.

In conclusion an ethical statement was presented which emphasizes that is is the responsibility of the qualified clinical investigator to develop the concepts and to do those studies that will improve the quality of life. The question was raised whether or not we have any right to withhold studies that can improve life and the quality of life.

Finally, major recommendations are that, without question, maternal and juvenile components be considered significant requirements for any support to diabetic centers. Pseudo-neonatologists and obstetricians are to be discouraged in this field. The diabetic center should not be controlled, dominated and under the sole direction of departments of internal medicine, biochemistry and physiology. The concept of a high risk ward and the cost benefit of early hospitalization of diabetic or high risk mothers requires clarification. One should evaluate the savings in preventing the need for intensive care nurseries and high cost care as demonstrated in the high risk ward in Dallas and reported at this meeting by Dr. Whalley. The final recommendation is the need for a forum where the obstetrician, pediatrician and internist who are interested in diabetic pregnancy and the infant of the diabetic mother can be encouraged to meet, exchange ideas and develop research protocols on a regular ongoing basis.

RISK OF INFANT MORBIDITY INCREASED

Maternal:
1. Vascular abnormalities
2. Poor metabolic control - Ketoacidosis - Coma
3. Pyelonephritis, clinical
4. "Neglectors"

Pregnancy:
1. Toxemia
2. Placental Insufficiency
3. Fetal Distress - estriol
4. Fetal Maturity S/L, fat cells, creatinine, etc.

Delivery:
1. Maturity & size - ultrasound
2. Gestational Age - < 35 wks. "Stress" test

Condition at Birth of Infant

NEEDS

1. Fetal
   metabolic, physiological

2. Perinatal
   Optimal Adaptation
     & Intervention

3. Neonatal
   Metabolic, Functional
   Environmental
   Emotional & Behavioral

4. Long-term
   Metabolic
   Behavior, Development
   Growth, nutrition

CLINICAL COURSE AND FREQUENCY IN PER CENT

COMPLICATIONS (b, b, c)

	IDM*		IGDM**	IDM & IGDM (B)
Uneventful Course	50		·80	--
Respiratory Distress	30		10	20
Hypoglycemia	60		16	56
Symptomatic	20		10	--
Hypocalcemia	25		15	18 (<7 mg%)
Polycythemia	40		30	34
Hyperbilirubinemia	50		25	35
Heart Failure	10	17▽	?	--
Renal Vein Thrombosis	?		?	2.4
Transient Hematuria	8		8	--
Congenital Anomalies	10		3	8

* Infants of Insulin Dependent Diabetic Mothers

** Infants of Gestational Diabetic Mothers

▽ Ref (e, e)

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<u>Prevention</u>:

1. Fetal, perinatal morbidity & mortality
   "Optimal" perinatal care

2. Congenital abnormalities

3. Aberrant mothering
   C-Section, I.C.N.

4. Fear of and actual diabetes mellitus

5. Abnormal growth, development, nutrition,
   behavior

Environmental Factors ⇌ Metabolic Fuels ⇌ Hormones

Temperature	Glucose	Levels Actions
Oxygenation (Redox)	FFA, Glycerol	Insulin
Stimulation	Ketones, Lactate	Glucagon
Feeding	Amino Acids:	G.H., Somatomedin
	branched chain	Corticoids
	alanine	Parathyroid
	glutamine	Thyroid
		Catecholamines
		(DBH)
		FSH, LH, HCG
		Estrogen, Testost.
		Hypothalamic
		factors (10)

INDICES OF FETAL MATURATION

Philip M. Farrell, M.D., Ph.D.

Fetal maturity, for practical purposes, may be defined as a state in which critical organs of the developing organism have differentiated structurally, metabolically, and functionally such that adaptation to extrauterine existence may be accomplished without intensive medical intervention. The importance of accurate prenatal identification of fetal maturity cannot be overemphasized, particularly in complicated pregnancies such as those represented by patients with diabetes mellitus. Although complete differentiation of the fetus is unquestionably achieved by complex series of developmental events involving multiple organs, common clinical experience and large body of epidemiologic evidence supports the view that the critical, and at times limiting, factor in prematurely delivered neonates is the respiratory system (1). Thus, unless the lung has reached a stage characterized by enhanced synthesis and secretion of pulmonary surfactants (2), premature delivery almost invariably results in the respiratory symptoms of hyaline membrane disease (respiratory distress syndrome or RDS).

Intensive efforts in recent years have been directed toward devising laboratory tests on amniotic liquid which would satisfy the need for reliable, prenatal demonstration of fetal maturity. Methods either used clinically or under investigation include techniques which assess cell characteristics, fluid color, protein content, urea and uric acid concentrations, creatinine level, and phospholipid composition (3). Creatinine measurements have been widely used but the rise in the amniotic fluid concentration of this substance after 35 weeks gestation relates to development of fetal renal maturity (and possibly muscle mass) rather than to lung differentiation. Thus, the presumption that a high creatinine concentration in amniotic liquid implies the potential for extrauterine respiratory sufficiency has not proven valid. Further, it has become recognized that multiple factors independent of the fetus affect amniotic fluid creatinine including maternal renovascular disease, toxemia, and diabetes; these conditions "artifactually" increase creatinine and lead to overestimation of fetal maturity.

In view of the significance of the lecithin-rich surfactants in maintaining neonatal alveolar stability, it is not surprising that estimation of phospholipids secreted from lung into amniotic fluid has demonstrated a good correlation with postnatal respiratory function. The concept that the intra-amniotic contents could directly reflect fetal pulmonary maturity stemmed from experimental studies with ewes in the mid 1960's and from the subsequent finding of diminished lecithin in amniotic fluid obtained from a limited number of pregnancies resulting

in neonatal RDS. The major advance, however, came in 1971 when Gluck and associates (4) reported that RDS could indeed be "diagnosed" antenatally by measurement of the ratio of lecithin to sphingomyelin (L/S) in amniotic liquid. Since then, more than 100 reports have appeared in the literature, unequivocally confirming the clinical predictability of amniotic fluid phospholipids in the uncomplicated pregnancy and delivery (1). The key change in amniotic fluid that serves as an index of fetal lung maturity and forms the basis of all present, phospholipid-oriented tests is an increase in the concentration of lecithin. Since amniotic fluid sphingomyelin remains nearly constant as gestation advances, it may be used as an internal standard to permit calculation of L/S as an indicator of increased lecithin. Further, using the sphingomyelin concentration as a reference provides an amniotic fluid volume correction factor so that reliable measurements may apparently be obtained in cases of oligo- and polyhydramnios. The surge in L/S ratio reported by Gluck and co-workers and repeatedly corroborated by others, occurs between 34 and 38 weeks gestation (1). In terms of predicting pulmonary maturity, the critical L/S value approximates two, i.e., a lecithin concentration twofold greater than sphingomyelin. Indeed, a review of more than 1,000 individual cases of uncomplicated pregnancies in the literature revealed that L/S values greater than two are associated with an RDS occurrence rate of nearly zero (1). Such reproducibility led Farrell and Avery (1) to conclude that "a properly determined amniotic fluid L/S ratio greater than two indicates, with a probability of nearly 100%, that on uncomplicated, vaginal delivery, the infant will not develop hyaline membrane disease."

Development of the respiratory distress syndrome continues to be a major problem in infants of diabetic mothers (IDM). Data from large series of diabetic pregnancies of unspecified gestation indicate that RDS incidence figures are approximately 20 fold greater than those found in normal pregnancies (1). In fact, with the exception of congenital anomalies, pulmonary hyaline membranes are said to be the most common pathologic finding in IDM at autopsy. Several possible mechanisms have been suggested to explain this phenomenon including increased incidence of prematurity, delivery by cesarian section, perinatal asphyxia, as well as the effects of the metabolic abnormalities of maternal diabetes leading to fetal hyperinsulinemia, macrosomia, and increased body fat. Although some evidence suggests that the association of diabetes and RDS is simply attributable to the obstetric practice of premature delivery by cesarian section, rather than to the carbohydrate disorder per se, a recent study (5) which controlled for gestational age, mode of delivery, and other risk factors, suggests that the increased incidence of RDS in IDM can be directly related to maternal diabetes.

A number of reports have recently appeared attempting to define the pattern of amniotic fluid phospholipids in the diabetic pregnancy. This

approach could theoretically answer the question of whether or not the inherent risk of developing RDS is high in diabetic offspring. Unfortunately, the results of studies where the ratio of lecithin to sphingomyelin in amniotic fluid has been determined as a function of gestational age present a confusing picture. Some findings support the impression that amniotic fluid phospholipid patterns are unaltered in diabetic pregnancies, whereas others suggest that the surge in L/S might be either abnormally early or late, depending upon the severity of maternal diabetes (6). Because of discrepancies in the literature on the ontogeny of amniotic fluid lecithin, it is not possible at present to draw definitive conclusions regarding this question. It is pertinent to note, however, that a controlled study in the non-human primate model of the glucose intolerant pregnancy (the Rhesus monkey treated with streptozotocin) demonstrated an acceleration in the time of appearance in gestation of high L/S ratios (7).

With regard to specific indices of fetal pulmonary maturation in diabetic pregnancies, the most significant issue uncovered to date has dealt with the reliability of a high (greater than two) L/S ratio in predicting the absence of respiratory distress syndrome. The results of at least 6 recent clinical investigations have now documented that "mature" L/S ratios are not associated with the same low incidence of RDS when maternal diabetes complicates the pregnancy. In fact, the majority of the false positive L/S ratios found by this author in reviewing the literature have been in infants of diabetic mothers. Statistical confirmation of the higher incidence of RDS with L/S ratios greater than two has been demonstrated by Donald et al. (8) in a large series of normal and complicated gestations. Their results and those of Dunn et al. (9) suggest that L/S ratios greater than two are associated with RDS in 7-18% of IDM; this occurrence rate is approximately 100 fold greater than the incidence observed in non-diabetic pregnancies delivered with "mature" L/S ratios. Information regarding the other widely used index of pulmonary maturity, the shake test, is insufficient to permit comment on the usefulness of this technique in complicated pregnancies.

The explanation for the failure of L/S greater than two to predict pulmonary maturity in IDM is not clear at this time. Some findings, however, suggest that insulin might play a role in pulmonary phospholipid metabolism (10). In addition, it is apparent from studies in the glucose intolerant Rhesus pregnancy that the fetal lung lecithin reservoir which is normally established in the final 10% of gestation may not develop in hyperinsulinemic fetuses despite the presence of an L/S ratio greater than two (7). The absence of such a reservoir could result in greater vulnerability to intra- and postpartum stress and therefore an increased probability of surfactant deficiency and RDS (1).

In summary, it is now established that extrauterine adaptation without intensive medical intervention is best predicted by tests which provide an index of the state of pulmonary maturity. Measurement of the lecithin to sphingomyelin ratio in amniotic liquid has proven to be the most reliable index and when greater than two in uncomplicated pregnancies, predicts the presence of mature respiratory function with nearly 100% accuracy. In contrast, the test has proven less reliable in diabetic pregnancies since high ratios are associated with a significant incidence of RDS. This observation emphasizes the need for anticipation of respiratory symptoms in IDM, even when delivery follows the demonstration of an L/S ratio greater than two. The failure of the Gluck test to predict fetal pulmonary maturity in gestations complicated by maternal diabetes indicates that further research is urgently needed on amniotic fluid lipids. In view of the importance of the highly saturated, surface active lecithins in neonatal pulmonary function, future investigational efforts should perhaps be devoted to a careful delineation of fatty acid composition of these compounds in amniotic fluid from diabetic pregnancies.

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RECOMMENDATIONS: DIABETES IN PREGNANCY

Roger K. Freeman, M.D.

Research: The following questions are in need of being solved.

1. What is the role of pregnancy in the acceleration (or amelioration) of diabetic retinopathy?

2. What is the relationship between diabetic control during pregnancy and outcome -- both immediate and long term?

3. What is the impact of the different hereditary forms of diabetes on pregnancy, the mother, the fetus, and the child?

4. What is a Class "A" diabetic and what outcome can be expected for the mother (long term), the fetus, and the neonatal and childhood development?

5. What form of screening should be done during pregnancy?

6. Is there any role for oral hypoglycemic agents in pregnancy? If answer is already clear, this should be publicized and controlled.

7. What evidence is there that estriol monitoring has value? Oxytocin stress testing? How should these be used?

8. What factors (if any) influence fetal maturation in the fetus of a diabetic? Do they have a different outcome even with good L/S ratios than nondiabetics? Is the A,B,C, diabetic really different from the D,E,F, and R groups with respect to fetal pulmonary maturity?

9. What is an abnormal GTT in pregnancy?

10. Do diuretics and/or low salt diets have any value in pregnant diabetics? Are they detrimental? If answers are now available publicize and control.

11. Is the administration of exogenous sex steroids beneficial?

12. Are oral contraceptives safe in diabetics?

13. Can neonatal hypoglycemia be influenced by terminal maternal glucose control by constant insulin infusion just before delivery?

It occurs to me that most of the above questions could be answered in studies done in a number of selected centers who would agree to manage pregnant diabetics by certain protocols designed to answer the questions. Since there is a considerable difference of opinion in management at this time, the validity of different approaches could be compared. In this same setting, training of obstetricians, internists, and pediatricians could be carried out with an eye to producing people trained to both manage such patients as well as to do continuing investigative work in this important area. In addition, the fallout from this would undoubtedly benefit all high-risk pregnant patients.

DIABETES AND PREGNANCY

Norbert Freinkel, M.D.

The effects of pregnancy on intermediary metabolism and diabetes
have constituted one of the major lines of inquiry in our laboratory for
a number of years. The continued commitment has been prompted by the
following considerations: First, pregnancy is one of the few physiological
situations in which a propensity for diabetes may become unmasked ("ges-
tational diabetogenesis") and the insulin requirements of known diabetics
increase. Thus, pregnancy may provide etiological insights into the
environmental factors which influence diabetes. It is becoming increas-
ingly clear that the placental elaboration of hormones with contrainsulin
properties (such as placental lactogen and progesterone) may be of im-
portance in this regard. Second, as first demonstrated in this laboratory,
pregnancy is attended by the development of a new insulin-degrading
structure, the conceptus, so that it may furnish a physiological setting
in which the effects of insulin catabolism upon insulin homeostasis may be
defined. Third, during pregnancy, a continuously-feeding parasite, the
fetus, develops within an intermittently eating host, the mother -- a
situation conducive to an exaggeration of the normal mechanisms for fuel
conservation and mobilization. Thus, analysis of the metabolic inter-
actions may yield new insights into normal as well as novel mechanisms
for regulating gluconeogenesis, lipolysis, nitrogen equilibrium, acid-
base balance, etc. In addition, the total dependence of the fetus upon
nutrients derived from the mother creates an unique opportunity for
testing the contributions of nature vs. nurture. Conceivably, clarifi-
cation of the impact of maternal environment upon the development of
fetal anlage (e.g., pancreatic islets, fat cells, neural tissues, etc.)
could furnish direction for ultimate biological engineering of the fetus
via metabolic manipulations of the gravid host. Finally, and in a more
pragmatic sense, perinatal mortality in diabetic pregnancies still hovers
in the 10-15% range. Better understanding of gestational changes in
intermediary metabolism may form the basis for more rational management
of pregnant diabetics and for improved fetal salvage in such obstetrical
conditions attended by "high risk."

The existing body of knowledge has been derived from research in vivo
with intact humans, subhuman primates, and smaller laboratory animals, and
in vitro with many cellular and subcellular preparations. Clearly,
pathophysiological insights have necessitated input from all of the
biological disciplines. Thus, recommendations for future growth in this
area must include appropriate support for the most basic as well as
clinical approaches.

ACTIVITIES OF THE EUROPEAN DIABETIC PREGNANCY STUDY GROUP

J. J. Hoet, M. D.

In order to have an interdisciplinary exchange of information concerning developmental biology as applied to diabetes, a European diabetic pregnancy study group was created.

The need for this group was felt by obstetricians working in diabetes, the internists dealing with pregnancy, the neonatologists involved in the care of infants of diabetic mothers, the physiologists or biochemists utilizing animal models, and pathologists. There was no common forum where these investigators could exchange experiences and through their mutual interests be further stimulated in their endeavors.

The group was established in 1968 and now consists of 25 members. The maximum number of members has been set at 50. The members were chosen from among European physicians, pediatricians, obstetricians, pathologists, and basic scientists with a primary interest in diabetes and pregnancy or developmental biology as applied to diabetes. These permanent members have the privilege to invite one guest to each meeting. Since the guests change every year new input is continually infused into the group.

The group meets once a year for two and a half days in a cultural setting where the members will not be disturbed by other activities. The last two meetings took place in Hasselby Castle in Stockholm where the Nobel Symposiums are held and in Europahaus Castle of the Vienna University.

The format of each meeting is established by three members who meet six months before the meeting. The membership of this committee is rotated so that all members eventually participate. This committee reviews the ongoing research in the field, and are also informed by each member of the group of their current interests. On the basis of this information, themes for discussion are chosen. Usually a theme for discussion in depth is presented, for example, animal models (rats, sheep, primates) and their relevance to humans. This discussion may take most of one day. Experts in the field will also have been invited. The remainder of the meeting is utilized for members to present and discuss their current research and interests. Ample time is allowed for discussion.

In addition, one or two lectures concerning research in the fore-front, for example, insulin receptors in the placenta and fetus, are

given by an expert in the field, in this case Dr. DeMeyts from NIH. The group has been privileged to welcome and to hear presentations of United States contributors such as Drs. N. Freinkel, R. Knopff, R. Chez, J. O'Sullivan, and A. Renold.

Part of the meeting is also set aside for discussions regarding criteria for the improvement of the delivery of health care. Thus, the activities of the group have resulted in an integration of research and concern for the clinical aspects of the problem. Another aim of the group has also been the improvement of teaching in the area of delivery of health care.

The Diabetic Pregnancy Study Group is operating under the auspices of the European Association for the Study of Diabetes. There have been several beneficial consequences of the activities of the group:

1. The members and guests have been stimulated by the opportunity to exchange ideas with experts and by the excellence and the simplicity of the meeting. Their interest in the field has been maintained.

2. The Diabetic Pregnancy Study Group has been solicited by national and European societies relating to perinatology and obstetrics to conduct postgraduate meetings in several countries in Europe. It may be estimated that the members of the group (including the local experts in their panel) conducted postgraduate meetings for three to four thousand physicians in Europe during the past year. The group has accepted the invitation of the European Association for Perinatology to organize a four hour postgraduate session in Uppsala, Sweden in 1976. The group does not publish their proceedings as they want free discussion without restraint. The group is financed partly by a pharmaceutical company (Novo Foundation). A two-year grant has been received from the Wellcome Foundation which covers expenses for the invited guests. The group feels that it has achieved a comprehensive and integrated goal which has impact on the teaching of delivery of health care in the field of diabetes and pregnancy in Europe.

EFFECTS OF ORAL CONTRACEPTIVE AGENTS
ON CARBOHYDRATE AND LIPID METABOLISM

R. K. Kalkhoff, M.D.

There is little evidence to indicate that conventional oral contraceptive agents induce overt diabetes in healthy women. In 22 prospective studies involving 867 subjects, the over-all incidence of diabetes was only 3.9% and 15 out of the 22 studies reported no incidence of the disease.

Nevertheless, there is substantial data to indicate that diabetogenic stress does attend administration of the pill in such individuals. First, plasma glucose responses to oral glucose, though normal, are significantly higher than among non-pill users. Secondly, plasma insulin responses are higher than normal, suggesting some degree of contra-insulin effect. Finally, the incidence of impaired steroid glucose tolerance stress tests is 10-20-fold greater than in a control population.

From an epidemiological standpoint, it is imperative to define the extent to which these subtle changes, verging on a reversible form of subclinical diabetes, constitute a health risk. It is necessary to consider these changes in a metabolic setting that is also known to raise blood pressure, increase plasma lipids and promote some degree of predilection to vascular accidents.

In women with pre-existing diabetes, the majority of investigations have shown a worsening of carbohydrate intolerance, especially in sub-clinical and maturity-onset types. Insulin-requiring patients demonstrate variable responses: some become quite labile and difficult to control; others are affected minimally. In this situation future studies must ascertain whether these risks outweigh the risks of pregnancy or dictate the use of other methods of contraception or refinements of present oral agents.

To date additional clinical assessments of the estrogen and progestin ingredients commonly employed in the pill have not determined whether one class of compound is more diabetogenic than another. Prospective studies of subjects receiving oral estrogens alone (mestranol, ethinyl estradiol, diethylstilbesterol, Premarin, etc.) or oral progestins derived from either nortestosterone or 17 alpha hydroxy progesterone have uncovered no definitive ranking of their contra-insulin action. Clinical pharmacologists must direct more attention to this area of research if this question is ever to be answered.

A major paradox that now exists in this field is the apparent contrasting effects of natural estrogens, on the one hand, and semisynthetic estrogens, on the other, with respect to their influence on carbohydrate tolerance. There is abundant literature to indicate that natural hormones like estradiol, when given parenterally, tend to improve carbohydrate tolerance in a variety of animal species including man. Oral administration of other kinds of synthetic estrogens seems to have an opposite effect. This problem area constitutes another opportunity to relate a specific steroid to its specific effects on glucose metabolism. This will require a concerted effort on the part of both clinical and basic scientists.

At a tissue level, it is known that most estrogens and progestins at some dosage level boost plasma insulin, enlarge pancreatic islets, have profound effects on hepatic and peripheral tissue carbohydrate and lipid metabolism. Precise mechanisms remain to be defined. In some instances when glucose tolerance is disturbed, there appears to be a gluco-corticoid-like action. Indeed, the enhancement of gluco-corticoid effects by estrogens is well known. In other instances, when carbohydrate tolerance improves, there are insulin-like effects on a variety of tissues including liver, muscle and fat in association with induced hyperinsulinemia. From this standpoint, research must differentiate anti-insulin from insulin-like and relate these changes to specific compounds and steroid structure. The outcome of such studies will help to develop improved contraceptive hormones for use by normal and diabetic women and may actually uncover agents that might be employed in the treatment of diabetes and related health disorders.

Most estrogens increase plasma lipids; some progestins lower them. Increasing attention is being devoted to the interplay of these hormones on hepatic synthesis and release of lipids and their carrier apoproteins from liver and the action of these hormones on peripheral tissue lipases and peripheral turn-over of triglyceride and cholesterol. This research is still in its early stages. Much financial support for this line of investigation is also needed for reasons similar to those outlined above. A basic understanding of these mechanisms may lead to production of anti-fertility compounds that lower, rather than increase, plasma lipids and the risk of vascular disease among pill users and may eventually allow the development of compounds that improve pre-existing hyperlipidemias as well as diabetes.

Editor's note: for further information the reader is referred to Dr. Kalkhoff's article, Effects of Oral Contraceptive Agents on Carbohydrate Metabolism. J. Steroid Biochem. 6:949-956 (1975).

INFANT OF THE DIABETIC MOTHER

Mark A. Sperling, M.D.

The state-of-the-art pertaining to the infant of the diabetic mother has been elegantly reviewed. It need only be stressed that most of the stigmata of infants of diabetic mothers, and the complications to which these infants are subject, apply equally well to those infants whose mothers have gestational diabetes, a disorder affecting some 2% of pregnant women, as to those infants whose mothers are diabetic prior to pregnancy. Although as pointed out by Dr. Cornblath, Dr. Schwartz, Dr. Chez and others, much attention has focused on the disordered carbohydrate metabolism, hyperinsulimenia, large size, neonatal hypoglycemia, and hypocalcemia, prematurity, respiratory distress syndrome and its prevention by assessment of lung maturity, several aspects are poorly understood. Chief among these, it appears to me, is the high incidence of congenital anomalies. In a recent survey (Soler et al., Lancet 2:54, 1975) among 98 diabetic women, ten pregnancies ended in perinatal death, and of these seven could be attributed to congenital anomalies. The sequelae of fluctuating levels of glucose, amino acids and other nutrients, on organogenesis during critical periods of embryogenesis is unknown and further studies on an animal model are urgently required. One such model is the pregnant nonhuman primate in whom diabetes is induced by streptozotocin as described by Dr. Chez.

Animal models supporting the hyperglycemia-hyperinsulinemia theory to account for some aspects of fetal pathophysiology in maternal diabetes mellitus can and have been supplanted by direct evidence in humans.

Employing constant infusion of glucose into mothers and the technique of fetal scalp capillary blood sampling after artificial rupture of the membranes late in gestation Brudenell and Beard have shown that:

1) The placental transfer of glucose in normal and diabetic pregnancies is explicable on the basis of facilitated diffusion with a fetal limit of approximately 170 mg/dl.

2) In normal women maternal insulin levels rise promptly whereas fetal insulin secretion in sluggish.

3) In contrast, in gestational diabetes, maternal insulin secretion is sluggish whereas fetal insulin secretion is prompt and highly significant (Brudenell, M., and Beard, R.: Diabetes in Pregnancy. Clinics in Endocrinology and Metabolism 1:673, 1972, W. B. Saunders Co.).

Furthermore, human fetal pancreatic islets secrete more insulin when grown in media containing high glucose concentrations than in media with low glucose (Goldbloom, Colle, and Brazeau, Diabetes, suppl 2, 421, 1975).

An additional parameter, hitherto relatively unexplored is the effect of maternal hyperglycemia on fetal glucagon secretion. In normal full-term infants there is a rapid significant rise in plasma glucagon concentration following delivery, and a brisk response to amino acids such as arginine or alanine (Sperling, et al. J. Clin. Invest. 53:1159-1166, 1974). In contrast, unlike the situation in adults, glucose infusions do not suppress neonatal glucagon concentrations, unless the glucose is infused concomitantly with insulin. Since the infant of the diabetic mother has relative hyperinsulinemia it might be anticipated that glucagon secretion is blunted. Indeed as recently shown in a preliminary report (Williams, P. R., Sperling, M. A., Racasa, Z., Diabetes, suppl 2, 24:411, 1975) both spontaneous and amino acid stimulated glucagon secretion is blunted in infants of diabetic mothers particularly in infants whose mothers require insulin. Conceivably, this blunting of glucagon secretion contributes to neonatal hypoglycemia. In an attempt to predict those infants who might be prone to develop hypoglycemia we have begun measuring glucagon levels in the amniotic fluid. Although glucagon is present in amniotic fluid, results are too preliminary to correlate the utility of the procedure. However, since amniocentesis is routinely performed to assess lung maturity via the L/S ratio, amniotic fluid samples are regularly available. In addition, in an attempt to study the potential sequelae of long term intrauterine hyperglycemia on the ontogenesis of liver cell-glucagon interaction, we have initiated studies of the binding of glucagon to liver plasma membranes and the generation of cyclic AMP in the fetuses and newborn pups of normal and diabetic rats.

These studies, eventually performed on human livers, might shed new insights into understanding the pathophysiology of disordered glucose homeostasis in infants of diabetic mothers. Other studies need to be performed.

1) Glucose turnover can now be estimated using non-radioactive isotopes and micro techniques directly applicable to infants.

2) The effects of constant glucagon infusion at doses known to raise levels to high physiological values on glucose homeostasis in infants of diabetic mothers can now be undertaken.

3) The potential role of amino acid infusions into mothers and/or their infants as a potential means of accelerating gluconeogenesis and glucagon secretion needs to be explored.

THE MANAGEMENT OF THE PREGNANT DIABETIC

Peggy Whalley, M.D.

The management of the pregnant diabetic in Dallas is for the most part quite similar to the management described by Dr. Younger and Dr. Carrington. Rather than repeat these same tenets, I would like to confine my remarks to those points where the management differs. First, I need to define the patient population and the facilities available to us for the care of the high-risk pregnancy. The majority of our pregnant diabetics are indigent patients of Dallas County who obtain their prenatal care in the clinics at Parkland Memorial Hospital (PMH). We do not routinely screen all patients for evidence of glucose intolerance, therefore, I have little experience with the significance or management of the so-called Class A gestational diabetic as discussed by Dr. Carrington. Thus, the experience at PMH is confined to the insulin-dependent diabetic with fasting hyperglycemia (Class B or greater). A certain proportion of the Class B diabetics, however, are gestational in the sense that prior to the pregnancy under consideration they were not known to be diabetic and in most instances the diabetes subsided following delivery, at least over the short-term postpartum follow-up. We are also fortunate to have a 28 bed ward at PMH exclusively for the care of the high-risk pregnant woman. Thus, we are able to admit to Parkland all those women whose fetuses are at risk and who would benefit from prolonged hospitalization with close clinical monitoring. The indigent pregnant patient with diabetes constitutes such a group, and for the past two-and-one-half years we have routinely admitted to PMH all pregnant diabetics at 32 weeks gestation, or earlier if indicated, where they remain until delivery.

The management of these patients is best illustrated by describing a single case summarized on the accompanying high-risk pregnancy sheet. This elderly, multiparous woman, with adult onset diabetes of nine years' duration controlled with oral hypoglycemic agents, had a past pregnancy history of four stillbirths. She was first seen in the clinic at 12 weeks gestation and was admitted at that time to the high-risk unit for initial evaluation. The oral hypoglycemic agent was stopped and she was easily controlled by diet with the addition of ten units of NPH insulin daily. She was then discharged to be followed weekly in the high-risk pregnancy clinic. However, she was a poor clinic attender and because of her poor past obstetrical performance as well as the obvious increasing insulin requirements as pregnancy advanced making clinic management difficult, she was admitted to the high-risk unit at 28 weeks gestation for terminal care. Her subsequent course is illustrated on the high-risk pregnancy progress sheet. She was placed on a 2,200 calorie diet and NPH insulin was increased to 65 units. On this regimen, the majority of fasting

plasma sugars were within the normal range and postprandial plasma sugars were in a satisfactory range. Serial sonography and clinical estimation of fetal size indicated good fetal growth. Her weight gain was normal and she remained normotensive. Renal function as evaluated by serial endogenous creatinine clearance and plasma estriols obtained twice weekly remained relatively stable. At 35 weeks gestation because of developing hydramnios, subjective evidence of decreased fetal movement and her past history of four stillbirths, an amniocentesis was performed. The LS ratio was greater than two and she was delivered by cesarean section of an apgar 9/9, 2,750 gram infant who has subsequently done well. As illustrated by this case, the general management of the pregnant diabetic at PMH includes:

1. Initial hospitalization at the first clinic visit for baseline studies and determination of insulin requirements.

2. Subsequent weekly visits to the high-risk pregnancy clinic with periodic adjustment of the insulin dosage.

3. Hospital admission at 32 weeks gestation for terminal care allowing close clinical monitoring and more rigid control of hyperglycemia.

4. Serial sonography every three weeks to monitor fetal growth.

5. Serial endogenous creatinine clearances to monitor renal function.

6. The oxytocin challenge test is occasionally used to determine fetal well being.

7. Serial estriols or serial HPLs are not obtained. Plasma estriols recorded in the example patient were obtained as part of a double blind study to determine the utility of plasma estriols as an indicator of fetal well being (Duenhoelter, Whalley, and MacDonald). The results of this study indicated that plasma estriols were of no value in our hands for the management of a diabetic pregnancy.

8. Low salt diets and/or diuretics are not prescribed. Studies by Gant and MacDonald and coworkers have shown that the metabolic clearance rate of dehydroisoandrosterone sulfate via conversion to estradiol in the placenta normally increases remarkably as pregnancy advances. For a variety of reasons, changes in the placental clearance of dehydroisoandrosterone sulfate almost certainly reflect primarily changes in maternal blood flow through the placenta. These workers have shown that the response to thiazide administration plus sodium restriction in pregnant patients is a dramatic decrease in the placental clearance of dehydroisoandrosterone sulfate. The implication of these findings is that maternal perfusion of the placenta was reduced appreciably. Therefore, in the absence of any impressive evidence that dietary restriction of

salt or the administration of diuretics is beneficial to the fetus, their use must be seriously questioned.

9. Our ultimate goal in management is to achieve a gestation of 37 weeks at which time amniocentesis for determination of LS ration is performed and if > 2 delivery is accomplished. If the fetus is not excessively large, age and parity not great, the cervix favorable, and the presenting part is vertex, delivery is attempted by oxytocin induction. If these criteria are not present or if labor is not promptly established, cesarean section is performed.

To date, a total of 50 pregnant diabetic patients admitted to the High-Risk Pregnancy ward have been delivered. Delivery was accomplished by cesarean section in 38 patients (78%). There were two stillbirths and two neonatal deaths, a perinatal loss of 8%. The two neonatal deaths included a 4,525 gram infant with congential heart disease who died 48 hours after birth and a 1,920 gram infant delivered following spontaneous rupture of the membranes and onset of premature labor. The infant died of severe hyaline membrane disease. The two stillbirths included a 900 gram fetus delivered of a Class F diabetic with severe hypertension and renal disease. Fetal heart tones were lost at 30 weeks gestation. The second stillbirth was a 2,460 gram fetus delivered of a Class C diabetic at 35 weeks gestation. At autopsy, this infant was found to have disseminated cytomagalic inclusion disease.

	No. of Patients	Stillbirth	Neonatal Dealth
Class B	36		2
Class C	11	1	
Class D	2		
Class F	1	1	—
	50	2	2

In summary then, I feel that the management of the pregnant diabetic must be highly individualized and directed by a team of physicians who are skilled in the management of both diabetes and pregnancy. The practicing obstetrician who sees one diabetic patient every two to three years or the general internist not familiar with fetal-maternal medicine should not attempt to manage these patients without consultation. At delivery, a physician skilled in the care of the newborn whose mother has diabetes should assume primary responsibility for care of the infant. The availability of serial plasma or urinary estriols, serial HPL determinations, oxytocin challenge tests, and electronic fetal monitoring during labor to assess fetal well being are often given credit for the recent decrease in the perinatal mortality rate of this complication. However, it is difficult not to at least recognize that the increased fetal survival may well be the result of (1) the increased awareness of the high-risk pregnancy in general, (2) the development of centers devoted

to the care of these patients, (3) the establishment of intensive care units where the newborn of the diabetic mother can be closely monitored, and (4) the marked advances in the management of hyaline membrane disease, a major cause of neonatal death in former years.

Unit # _____

Name _____

Address _____

Birthdate _____

Classification _____

OP   ER   IP   Admit # _____

LNMP **8/17/73** Quickening **?** EDC **5/24/74** FHT 1st **?**

Complications **38 LA G8P7 Diabetes Dx 1965 – Orinase**
4 Stillborns: 1963 ? 1965 9# 2oz 1967 5# 2oz
1970 3# 3oz

		2/25	3/5	3/19	3/26	4/2	4/11	4/16			
Dates											
Weeks of Gestation		28	29	31	32	33	34	35			
	Weight	143	143	148	153	157	155	155			
	Blood Pressure	110/80	110/80	114/80	110/80	108/60	124/70	110/70			
	Hematocrit	34				35					
Renal Function	Plasma creatinine/urea										
	Urine Creatinine mg%/total		0.8/8			0.8/8					
	Creatinine Clearance		114			100					
	Urine protein	N	1+	N	N	1+	N	H			
Ultrasound	Biparietal (cm)		74		82		89				
	Growth Rate				2.6		2.3				
	Gestation		29		32		36				
	Placenta		post								
	L/S							>2			
	INSULIN	10	25	45	65	65	65	65			
	ESTRIOL	2.2	2.2	2.9	3.6	2.9	2.9	4.3			
	Clinical Estimated Fetal Weight			3½	4½	5	5½	6			

DELIVERY **4/19/74** (Date) **C-Hyst** BIRTH WEIGHT **2750** **9/9** gm

Newborn Outcome	Normal	Stillborn	Neo. Death	Dysmature	Premature	Morbidity Yes | No
	✔					

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DENTAL CONSIDERATIONS IN DIABETES MELLITUS

Robert Gottsegen, D.D.S.

That there is a relationship between diabetes mellitus and dental
disease is by now generally accepted. However, the nature and mechanisms
of that relationship are still unclear. Epidemiological and clinical
correlation studies are just beginning to reveal significant linkages,
thanks to the accumulation of meaningful data which can be subjected to
statistical analysis. For example, before 1956 when the first reliable
index of periodontal disease was developed (1), all estimates of perio-
dontal disease incidence and severity were subjective and variable
clinical assessments. In addition, the still rather recent concept of
prediabetes has cast doubt on the validity, in earlier studies, of
controls who were supposedly nondiabetic.

Diabetes mellitus in its interaction with the teeth and mouth may be
considered in four general sections: (1) the effect of diabetes
mellitus on the oral tissues and teeth; (2) the effect of dental disease
on diabetes; (3) the interaction of dental and medical therapy in the
diabetic patient; and (4) oral and dental manifestations as clues to
the presence of diabetes and prediabetes.

Physicians have long been familiar with the fact that oral changes
may be the first to suggest the presence of diabetes. For instance, dry
mouth is a frequent primary presenting symptom (2).

Other oral changes which may be found, aside from the purely dental
which we will discuss in greater depth, are hypertrophy of the lingual
filiform papillae and enlargement of the tongue (3,4,5).

Oral fluids reflect elevated blood glucose. Accumulating evidence
indicates that salivary glucose increases significantly as blood glucose
rises as, for instance, in glucose loading (6,7). The range of glucose
levels in parotid and pooled saliva of diabetics may be double that in
nondiabetics, 0.45-6.3 mg/100 ml for diabetics, vs. 0.2-3.3 mg/100 ml
for nondiabetics (8,9,10).

Also, the glucose content of gingival fluid is elevated in
diabetics when the blood glucose is high (11).

It is difficult to imagine that elevated glucose levels in the fluids bathing the teeth of such a small order of magnitude as this would have any great effect on increasing the caries rate, although it is possible. However, it is intriguing to consider how it may influence the microbial flora of the mouth, the bacteria of the plaque and particularly those organisms deep down in the base of periodontal pockets. For glucose is a nutrient in the bacterial milieu. It has been shown, for instance, that the growth of candida in saliva is restricted by competition with salivary bacteria for available nutrients and when glucose was added unrestricted growth of candida took place. Saliva from patients with well controlled diabetes showed good correlation between salivary glucose and growth of candida. Increased incidence of thrush in diabetics is due to high levels of glucose in saliva, which is the factor that limits candidal growth (12).

Caries. Caries is no more nor less of a dental problem in diabetics than it is in nondiabetics. Since most diabetics under treatment are on a regulated diet of some type with restricted carbohydrates, particularly juvenile diabetics who are in the age range where caries attack is greatest, they are, in fact, on a caries control program. Therefore, their caries incidence may be reduced when the diet is carefully controlled (13-15,24-27).

Diabetic experimental animals, on the other hand, do show increased incidence and rate of progress of caries compared to their nondiabetic controls on the same diet (16-23).

Relationship to Periodontal Disease

Uncontrolled Diabetes. An unusually high incidence of periodontal disease, including a striking number of severe cases, is noted in uncontrolled diabetics, particularly in those of the juvenile type (14,15, 28-36). The periodontal tissues are the supporting and surrounding tissues of the teeth, i.e., gingiva, periodontal ligament, alveolar bone. The periodontal disease of major concern consists of combined inflammatory and degenerative changes which range from a mild gingivitis through progressive deepening of the gingival sulcus (the space between the gingival collar and the tooth) and resorption of the alveolar bone housing around the root of the tooth to an advanced suppurative periodontitis ("pyorrhea") (15,34,35,37,38). These disease changes are not unusual or unique in any way when occurring in the diabetic individual, nor are there any pathognomonic histological findings (38-40). The disease seems to be similar in every respect to that found in nondiabetic individuals except for the large number of advanced cases and the significant frequency of cases of rapid and severe onset and progression, both unusual for this young age group.

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Space does not permit discussion of the experimental animal research except to note that the results are conflicting (21,23,40-48). Those animal species which develop diabetes spontaneously or genetically seem to have severe periodontal disease as part of the picture (21,42-48) but alloxan diabetic rats do not predictably show periodontal breakdown while pancreatectomized rats do (40,41,23).

Treated Diabetes. Both periodontal disease and diabetes become more prevalent with advancing age, which makes the evaluation of any relationship between them extremely difficult in the older-age groups. However, if the advanced type of periodontal disease generally associated with older individuals -- resorption of alveolar bone, tooth mobility, and pocket formation -- is seen with greater than expected frequency in young diabetic patients, the possibility of causal relationship is suggested. Between the ages of 18 and 40 diabetic individuals manifest a higher incidence of more severe periodontal bone resorption than can be attributed to local causes alone (4,14,49-53). Below the age of 18 there appear to be no premature resorptive bone changes attributable to diabetes (38,50,51,54,55) and above the age of 40 it becomes increasingly difficult to evaluate the correlation because so many patients are edentulous (14,50) (in itself possibly significant), or have periodontal disease. But in those who are not edentulous there appears to be no uniform relation between diabetes and alveolar bone resorption (49).

It is regrettable but understandable that most of the earlier clinical investigations of diabetes-periodontal disease association were either inadequate or not objective and thus are of limited value. However, despite their weaknesses, such as the limitations on their comparability, the absence of controls or the assumption of normality in the selection of controls, and the lack of a reliable reproducible method of scoring periodontal disease prior to 1956, from this group of reports one can distill the following conclusions. There seem to be two clinical periodontal syndromes related to diabetes. The first is the acute fulminating form found most frequently in the undiscovered and uncontrolled diabetic subject, particularly in the juvenile type, and characterized by gingival inflammation ranging from marginal gingivitis to acute suppurative periodontitis, mobility of teeth, pain on percussion of teeth, rapid loss of bone, granular subgingival proliferations, and multiple gingival abscesses. With control of the diabetes this group of symptoms may be expected to lessen in severity and occasionally to subside. The second is that of gradual resorption of the alveolar bone. This is a more chronic degenerative change which seems to be related significantly to the duration of diabetes. The concurrence of several workers in finding more frequent and more advanced bone loss in the 20-40 year old age groups where the diabetes may have been present for some years tends to support this thesis. In this dependence on the duration of diabetes for development of bone resorption there is a similarity to other so-called complications of diabetes such

as nephropathy and retinopathy (56). The possibility of correlation between the presence of degenerative periodontal breakdown and other diabetic complications appeared to be a fruitful area of investigation and is now being actively explored. For example, Glavind, Lund, and Löe in Aarhus demonstrated a greater loss of attachment and bone loss in those diabetics age 30-40 with retinopathy than in 30-40 year old diabetics with no retinal vascular changes (57). And in a study in Philadelphia (58), Finestone and Boorujy found not only an increase in prevalence and severity of periodontal disease in the diabetic patient but, in addition, a strong correlation between the periodontal index, duration of known diabetes and diabetic complications.

Not all epidemiological or prevalence studies agree (58-62), but it is usually possible to find weakness in experimental design in those which find no relationship between diabetes and periodontal disease.

Untreated or uncontrolled diabetics demonstrate interference with several aspects of their host defense mechanism such as polymorphonu-clear leucocyte mobilization (79,80,81), phagocytic activity (82), and some derangement of the bactericidal or bacteriostatic effect of blood against many microorganisms (83). These impairments in host resistance to infection have been related by some investigators to increased glucose levels in blood, tissue, and urine (79), but others have found them to be present in diabetics unrelated to the levels of either the blood glucose or the plasma insulin (81). There is agreement that they occur regularly with ketoacidosis (80). Thus, it may be a reasonable assumption that a great many diabetics, presumably those with elevated blood glucose, and most likely those with ketoacidosis, could have a reduced capacity for bacterial killing (83), resulting, among other things, in more severe periodontal disease.

Microvascular lesions, similar to those found in other organs and tissues, are also found in the gingiva and alveolar mucosa (63-73). The reliability of microvascular disease in the periodontal tissues as an indicator of diabetes or prediabetes is still in doubt. The subject of microangiopathy in relation to gingiva and diabetes will be discussed by D. Walter Cohen in another paper in this Workshop.

Microangiopathy (63-73), by decreasing the blood flow to peripheral tissues, may not only hamper granulocyte mobilization, but it may also result in decreased oxygen tension in the tissues and thereby set the stage for proliferation of anaerobic organisms. Since the importance of the gram negative anaerobic flora in plaque and in rapidly destruc-tive periodontal disease has received such emphasis in periodontal research recently, it is particularly intriguing to speculate on: (1) what effect the elevated glucose levels in saliva and gingival fluid has on these microorganisms; (2) whether each of the frequently recurring episodes of hyperglycemia and ketoacidosis in the juvenile

type, or "brittle," diabetic results in a burst of activity of the gram negative anaerobes as the host defenses weaken during these periods (81, 83); (3) and whether the tissue destructive products of these micro-organisms coupled with impaired collagen metabolism in the periodontal connective tissue (74,75) results in incremental periodontal destruction, each episode of which may be small but irreversible and thus cummulative.

Each one of these questions requires testing. If found to have some validity they could fit together to make up a hypothesis for the pathogenesis of periodontal disease in diabetics, consistent with the clinical patterns and epidemiological observations.

Effect of Dental Disease on Diabetes

Dental infection has been implicated repeatedly in the worsening of the diabetic state. Its presence will elevate the blood glucose, may cause ketoacidosis, and has been known to precipitate coma. The initial regulation of a newly detected diabetic patient may be rendered diffi-cult or impossible in the presence of active periodontal or apical infection. Furthermore, exacerbation of dental infection may throw a well-controlled diabetic patient out of control. Since in this disease a dental emergency may rapidly become a medical emergency and may endanger the life of the patient (15), it is of utmost importance that dental and periodontal health be established and maintained.

One additional factor should be mentioned. Gram negative bacterial infection might be expected to pose special problems for the diabetic patient since endotoxins have been shown to exert significant effects on glucose metabolism. In experimental animals the most consistent effect of endotoxin administration is hyperglycemia and depletion of liver glycogen (83). Periodontal disease is noteworthy (or notorious) for the prominence of gram negative organisms in its microbiological aspects. Endotoxin from these organisms has been extensively studied and endotoxin and the results of endotoxin activity have been found in the periodontal tissues.

The presence of rampant dental disease may influence the problem of systemic management of diabetes in yet another way by making mastica-tion painful or difficult. The patient may then turn to foods which are easier for him to cope with but which may be dietetically improper. With the loss of many or all of the teeth the masticatory problems are self-evident. Although full dentures may be satisfactory in many cases, they tend to become less so when the alveolar ridges on which they rest are resorbed, flat, delicate, or tiny. The alveolar bone resorption of periodontal disease may lead to such inadequate ridges by the time the teeth are lost, and the impression is gained that the

majority of diabetic patients who are edentulous have become so through periodontal disease. Furthermore, it has been noted that full dentures may not be tolerated well by the diabetic individual, particularly one who is poorly controlled, because of mucosal soreness and the need for frequent relining of the denture. Thus, it is wise not to hasten the consummation of the edentulous state in the diabetic patient but rather to make every effort to preserve a healthy, functional, natural dentition so that the proper foods may be chewed efficiently and comfortably.

Interaction of Dental and Medical Treatment

When it is discovered that a patient with advanced dental disease also has diabetes, extractions should not be performed, unless absolutely necessary, until the systemic condition is brought under control. Acute abscesses, however, require immediate drainage (84). Complete regulation of the diabetes may not be possible while dental infection is still present, but the glycemia can be reduced. With the amelioration of the diabetic status there may be dramatic improvement in the acute periodontal condition. The teeth may become firmer, gingival inflammation may subside, suppurative exudate from the gingival crevices may decrease, and soreness and sensitivity may lessen. At this stage dental evaluation may be carried out and necessary treatment instituted. Teeth in a hopeless condition may now be extracted and residual infection and inflammation eliminated. Periodontal therapy may lower the insulin requirement and reduce fluctuating uncontrollable sugar levels to a more manageable state. Thus, the treatment of periodontal disease may facilitate the practical regulation of diabetic patients (36,85-90).

Oral and Dental Manifestations as Clues to Presence of Diabetes and Prediabetes

A number of diabetes detection surveys of dental populations using the three hour glucose tolerance test have been conducted with somewhat confusing results. The University of Alabama group reported (91-98) that 43 out of 100 dental patients selected at random had frank or marginal abnormalities of their glucose tolerance curves, a surprisingly large number. When the results were analyzed for a variety of correlations it was found that significantly decreased glucose tolerance occurred in these patients with dry mouth, burning mouth, tooth mobility, and alveolar bone loss, either alone or in combination. A University of California study (99) tended to support the Alabama findings. However, other diabetes detection surveys of groups of dental patients using urinalysis (100), fasting blood sugar (101,102), or the glucose tolerance test (103) failed to reveal significantly larger numbers of diabetic individuals than in the general population. This is still an open question.

Clinical Considerations and an Appraisal

There are several different categories of the clinical situation in which the dentist or periodontist may encounter the interrelationship of diabetes and periodontal disease.

1. (a) A known maturity-onset diabetic, under treatment and controlled, usually an older individual, presenting for periodontal care of periodontal disease that is within the distribution norms of age and severity. This is not a diagnostic challenge, but rather a matter of management of the systemic condition during periodontal therapy which requires the close cooperation of the physician and dentist. The prognosis of the periodontal disease often seems to be adversely influenced by the coexisting diabetes although, as pointed out above, in the older age groups it is difficult to establish a relationship between the two conditions.

    (b) A maturity onset diabetic, under treatment, but whose diabetes is brittle and largely out of control, or a juvenile type, with newfound periodontal disease. There may be severe gingival inflammation, infection, and abscess formation. This is similar to the problem of periodontal disease in a previously undiscovered and, therefore, uncontrolled diabetic. In such a case, the clinical challenge is to control the acute periodontal infection which may then aid in the medical regulation of the diabetes.

2. A patient who has been under periodontal treatment and maintenance for some time and who develops diabetes. In this situation the establishment of the diagnosis of the preexisting diabetes may serve to shed some light on the way the periodontal tissues responded to previous therapy and from that point on the need is for enlightened dual clinical management.

3. The patient who presents with either severe acute suppurative periodontitis or advanced chronic periodontal disease at an unusually young age, who has positive physical symptoms of diabetes or a positive family history, and who, upon testing, is revealed to be diabetic. Since up to that moment his diabetes has been unrecognized and untreated, priority consideration must be given jointly to the medical control of his diabetes and the management of the dental infection.

4. The patient with advanced periodontal disease or with periodontal disease that is inexorably progressive despite the most thorough

therapy, who has a close family history of diabetes, but whose glucose tolerance curves are repeatedly within border-line or normal limits. This patient must always be regarded with suspicion as one who may develop diabetes. It may not be so quixotic to arbitrarily classify such a patient as a prediabetic.

Our experience, and that of a number of other clinicians working in this field, has led us to adopt the following beliefs as a clinical point of view, as of this date:

1. Certain oral and dental signs and symptoms, appearing singly or in combination, may be of value as clues to the presence of diabetes and prediabetes. These are dry mouth, burning mouth, tooth mobility, and alveolar bone loss. The most suggestive condition is one in which a young individual has rapidly advancing unexplained periodontal breakdown or steady inexorable breakdown despite the best therapy.

2. The degree of significance of these clues becomes greater if the individual has a positive family history of diabetes.

3. Just as increased fetal mortality and the birth of babies weighing more than 10 pounds occur more often in prediabetic mothers (104), just as recurrent hypoglycemia may be an early hint of a subsequently developing diabetes, just as retinopathy, nephropathy, or the absence of deep reflexes (105) may be the initial findings in a patient without overt symptoms of diabetes, so may these dental findings stand in relation to prediabetes and diabetes.

After-Thoughts

I would like to point out, in conclusion, that many of the statements that have been made about diabetes also apply to periodontal disease. For example, as Cahill has written (106), "Diabetes Mellitus is a syndrome composed of a sequence of events about which there is considerable knowledge in the middle and a gross lack of knowledge at either end." Just substitute the term "periodontal disease" for "diabetes mellitus."

In summary, it appears that several of the biological alterations associated with diabetes may be operative in the pathobiology of periodontal disease. These phenomena may, for any individual case, enter into the etiological assault singly, in various combinations or in varying proportionate strengths.

To those already mentioned we may add one more, possibly the most fundamental, that is, heredity. While it is generally agreed that heredity plays an important role in determining the susceptibility to diabetes mellitus and, as Steinberg and Rimoin (107,108) have written, the familial aggregation of diabetes has been known for centuries, in periodontal disease the role of the hereditary component is still not so clearly recognized. Yet many astute clinical observers in periodontics believe that there is some kind of genetic influence. Family tree, ancestral and kinship studies have not been worked out for periodontal disease, so this clinical impression cannot be factually supported. Furthermore, all the difficulties which have been described by Rimoin (108) in the investigation of the genetics of diabetes mellitus apply equally well to periodontal disease:

1. The definition of a periodontal disease patient, that is one with simply the sequelae of long-acting inflammatory disease due to the interaction of bacterial, inflammatory, and immunological phenomena vs. one with altered tissue response who shows advanced breakdown at an early age, often with only apparently mild irritants. Is the age at onset the important clue in the diagnosis of the genetically determined periodontal disease? Or is it the rapidity of progress?

2. Difficulties in definition of an affected relative. Asking a proband whether any of his relatives had "pyorrhea" or "periodontal disease" is unsatisfactory because in the past many teeth were extracted wholesale and many individuals rendered edentulous unnecessarily or for the trivial reasons, often unrelated to the presence of generalized periodontal disease.

3. As is diabetes, so is periodontal disease a condition of marked clinical variability. The periodontal disease tendency appears to be modified by a variety of factors including plaque accummulation, the occlusal or biting stress on the teeth, iatrogenic factors such as poor dentistry, and a wide assortment of other variables. Furthermore, as does diabetes, periodontal disease may have its onset at any age, so that at a given time only a fraction of the people with the heritable trait may be recognized.

4. Another difficulty for the geneticist is the high prevalence of the disease in the population.

5. Rimoin has stated, "The most important impediment to a proper genetic study is the fact that the basic defect in diabetes is unknown. Because of this, there is no certain method for detecting 'prediabetics'" (108). This is equally true for periodontal disease and thus, until a reliable marker for preperiodontal disease is obtained conclusive genetic studies will not be possible.

And yet, despite all these difficulties, it is our clinical impression that there may be some validity in paraphrasing Steinberg (107) as follows: Both frank diabetes and frank periodontal disease appear to depend upon the interaction of genetic predisposition and environmental factors. Thus it is reasonable to expect that some individuals who are genetically predisposed to develop (either) diabetes (or periodontal disease) never do so, even though they live to an advanced age, when the environment is maintained <u>sufficiently</u> stress and irritant free, i.e., no plaque (bacteriological and immunological etiologies minimized), good dental occlusion and function and no caries (mechanical irritants, food impactions, and physiological stresses minimized), good nutrition, and no harmful habits.

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SOME IMMUNOLOGICAL ASPECTS OF ISLET
TRANSPLANTATION IN THE RAT

Clyde F. Barker, M.D.

Most problems related to transplantation of tissues fall into two categories: (1) technical and logistical and (2) immunological. Early work in our laboratory dealt with technical obstacles in achieving cure of streptozatocin induced diabetes in rats by means of isolated islet isografts. The technique in rats is now reasonably satisfactory but the more difficult technical aspects of human islet isolation will require considerably more investigation.

Recent and current research in our laboratories is concerned with immunological aspects of islet transplantation, using the rat as the experimental model. An initial hope was that islet allografts, because of their endocrine nature, might prove only weakly antigenic (as has been found with ovary and parathyroid) so that rejection might either not occur or be easily overcome. The finding that islets carefully separated from collagenase digested pancrease and injected into allogeneic rats, sensitized these animals to subsequent donor-strain skin allografts, demonstrated that islets are antigeneic. The unexpected result that islet allografts between rats differing at the major Ag-B histocompatibility locus normalized blood sugars of diabetic recipients for only 2-3 days, seemed difficult to explain on an immunological basis, since such rapid destruction is atypical of classic rejection of any tissue. Several lines of evidence however indicated that the allogeneic islets were being destroyed by immune processes: (1) isologous islets survived for many months; (2) minimizing histo-incompatibility by using Ag-B compatible donors for islet allografts extended the post-transplant normoglycemic period to 8-10 days and up to 30 days if immunosuppression with antilymphocyte serum was employed.

To further clarify whether nonspecific factors such as damage during the isolation process or increased vulnerability during revascularization might result in anomalous early beta cell failure, islet allografts were studied in immunologically tolerant hosts. WF (prospective recipient) rats were injected at birth with ACIxWF bone marrow cells. Their tolerant status was demonstrated in adulthood by their acceptance of ACI skin grafts. After these animals were made diabetic with streptozatocin, 600-1200 ACI islets were injected into the portal vein. This treatment resulted in long term normoglycemia.

To determine whether vascularized allogeneic islets, well established in tolerant hosts, were still vulnerable to the immune process, WF lymphoid cells or WF anti-ACI serum were given to the tolerant

"cured" allograft recipients. Either immune serum or cells resulted in prompt destruction of the allogeneic islets and recurrence of the diabetic state, while the skin allografts were destroyed only by the WF cells, being resistant to destruction by anti-serum. Apparently pancreatic islets allografts are more sensitive to damage by humoral factors than are skin allografts.

The findings that islets are antigeneic and fully vulnerable to immune destruction - perhaps even more so than skin focuses attention on the necessity for optimal antirejection maneuvers in the case of islet allografts. One such maneuver would be the use of an immuno-logically privileged site. There is some evidence that the liver might be such a favored transplant site. Of 10 streptozatocin diabetic ACI rats treated with Ag-B compatible DA islets injected into the liver via the portal vein, 5 remained normoglycemic for > 30 days and 3 for > 80 days (MST 28.5 days). In contrast DA islets injected intraperitoneally were rejected more rapidly (MST 10.0 days).

If Ag-B incompatibility pertains, intrahepatic islets are rejected promptly (< 1 week) indicating that if the portal outflow tract is a privileged site it is an imperfect one. If histocompatibility is minimized, a privileged transplant site and mild immunosuppression might allow prolonged islet allograft survival.

Further investigation of islet allograft behavior in animals may provide valuable information regarding their probable fate in man. The rat is ideal for such studies since techniques for successful transplantation are established and because inbred strains allow definition of genetic requirements for success. The study of iso-grafts allows assessment of long term behavior of islets when the possibility of damage by rejection is excluded. It seems likely that animal studies will provide further insight into the unique patho-physiology of diabetes but animal models are probably not available for answering the most important question: Whether islet transplants can prevent the complications of human diabetes.

MONOLAYER CULTURE OF PANCREATIC BETA CELLS

William L. Chick, M.D.

Significant improvements in methods for preparing monolayers from newborn rat pancreas during the past two years have enabled studies of morphology and of insulin biosynthesis, storage and release by cultured beta cells. Characteristics of primary cultures closely resemble those in vivo. There is a high degree of longevity as evidenced by continued insulin release for several months. Although beta cell replication does occur, it is unlikely that this amounts to more than a small number of divisions per cell. This has made establishment of permanent cell strains extremely difficult. Overgrowth by more rapidly proliferating fibroblastic cells has been a complicating problem, although improved methods of preparation have enabled production of cultures containing 70 to perhaps greater than 90% beta cells.

Application of culture techniques has proven extremely useful both in basic and in applied research areas. Basic research problems currently under study in our own and in other laboratories include: 1. Detailed elucidation of factors controlling beta cell neogenesis; 2. Studies involving the interaction of beta cells with viruses; 3. Correlation of physiologic and biochemical data with cell morphology both at the light and electron microscopic levels. Applied research areas under investigation include the use of cultured cells for transplantation, and in addition as a basis for commercial insulin production.

In my opinion goals for the immediate future should include: 1. Development of more efficient methods for culturing beta cells, particularly from larger animals and from man; 2. Development of permanent strains of insulin-producing cells; 3. Continued exploration of the feasibility of using cultured cells as a transplantation resource, possibly in the form of a prosthesis incorporating cells in conjunction with artificial, semi-permeable membranes to prevent immune rejection; 4. Continuation of efforts to elucidate mechanisms controlling beta cell neogenesis since this appears to be a crucial factor in determining the onset and severity of spontaneous diabetes; 5. Use of cultured beta cells as a tool for investigating the possible role of immunologic mechanisms in the pathogenesis of diabetes.

I feel the aforementioned goals would best be attained by vigorous efforts to update our approaches to diabetes research in order to utilize more fully modern techniques of biochemistry and cell biology. Major emphasis should be placed on attracting biochemists and cell biologists from outside the diabetes community to collaborate in a

closely knit fashion with scientists specifically trained in diabetes research. Hopefully, such collaboration would generate a number of new, productive vantage points from which to view the various facets of the diabetes problem.

PANCREATIC TRANSPLANTATION

Marvin L. Gliedman, M.D.

The obvious present goal of pancreatic transplantation is to provide a simple, safe and effective primary treatment for diabetes of the juvenile onset type in order to abort or prevent the progression of the multi-organ complications of this disease. The experience in human pancreas transplantation since December 17, 1966 to date has been limited, with a total of only 47 known transplants reported to the ACS/NIH Organ Transplant Registry. The technics of implantation show a wide variety with one patient receiving a whole pancreas, 14 receiving a subtotal pancreas transplant, 6 receiving a subtotal pancreas implant plus a kidney, 6 receiving a pancreaticoduodenal and 20 receiving a pancreaticoduodenal and kidney. To this date the standards and technics of implantation continue to show variety, with segmental grafts and pancreaticoduodenal allografts transplanted most recently. Within the category of segmental grafts at least one of the recent allografts had a ligated pancreatic duct, the others employing either the duodenum or the ureter for exocrine drainage. The best technic in the human remains undecided. In considering the group of segmental pancreatic grafts with ligated ducts of Wirsung, there has been a high incidence of persistent pancreatic drainage. Suspected exocrine leakage via cut lymphatics which act as an accessory drainage system has been reinforced by intact duct closure seen at subsequent graft examination. It would appear to be a hazardous approach, now, to perform pancreas grafting without a technic to avoid the peripancreatic collection of protein rich pancreatic ferments that almost invariably will become infected in the immunosuppressed patient. The transplant of the pancreaticoduodenal graft is beset by problems related to the duodenal transplant. Exocrine drainage via a ureteral anastomosis to end of the pancreatic duct of a segmental graft has been successful in our hands but has had little usage by others.

While the early review of the patients was unclear with regard to pancreatic allograft rejection, it is now apparent that the pancreas does undergo typical rejection crises characterized by a low insulin output and impaired exocrine output, where these are monitored. It has been suggested that those patients who are less debilitated and non-azotemic are more liable to immune response affecting the gland.

The experience from 1966 has clearly demonstrated that the functioning vascularized pancreatic allografts of the segmental or total gland will correct the metabolic deficiencies of diabetes and free the patient from a need for insulin. Unfortunately, though 4 patients have progressed for time periods of 10, 12, 22 and 37 months

with functioning grafts, it is yet to be determined that the correction of the metabolic features of diabetes will stabilize or cause regression of the vascular complications of the disease. It appears important, in view of the predictable course of the nephropathy, that clinical investigations be carried out to determine if failing renal function can be stabilized or improved by a successful pancreatic allograft.

To this time pancreatic transplantation has taken place, largely, late in the disease process - sequential or with the transplantation of a kidney. Clinical protocols to evaluate the effect of the transplant in reversing or stabilizing established complications like nephropathy, are needed. Patients with failing renal function and signs of diabetic retinopathy should be transplanted to determine if the human pancreas recipient will cease the progression of the predictable diabetic nephropathy or reverse mesangial changes already established within the kidney at the time of transplantation. Serial conventional and electron-microscopy over prolonged periods of time to determine the true place of transplantation in this process are necessary. Fluorescein angiography to determine whether the vascular proliferative process of the diabetic will be affected by a pancreas transplant is also a necessary evaluation. Along with nerve conduction and muscle basement studies before and after successful long-term pancreatic allografting these will permit the crucial determinations of the relationship of a normal blood sugar and an intact pancreas on the diabetic. Whether diabetes is simply a malfunction of the pancreas (in toto or islets) or a generalized multi-organ process could be answered.

In the technics of the transplantation procedure proper, better preservation technics are needed since routine perfusion devices could recirculate potentially hazardous pancreatic secretions through the artery. Diverting acinar secretions during organ perfusion still allows contamination by the pancreas, of the bath, via the pancreatic lymphatics. The human preservation technics are still without "bench marks" for successful perfusion and predictability in well preserved tissue remote from the removal from the donor.

Clearly the development of methods to ablate acinar functions, while preserving structional and functional, intact islets, for both short and long term periods would be extremely useful. The accomplishment of this goal would determine, in the human, whether there is a need for continued acinar function for the long-term well being and integrity of the islets. It appears not needed in animals. With the capability of successful ablating acinar functions acutely for long periods there would be the ability to convert the pancreas transplant into a simple procedure requiring only the availability of an adequate artery or vein at any site in the body without the provision for

acinar drainage or the potential collection of enzyme rich fluid in the peritransplant area.

Finally, as they relate to the pancreas there is a need in the human to relate the role of the enzymes and hormones to rejection. The pancreas graft rejection appears clinically similar to acute pancreatitis along with a high incidence of venous thrombosis and graft loss early in the post-transplant period. Early methods of detection of pancreatic graft rejection as well as the best methods of treatment of pancreatic allograft rejection are still to be determined.

In spite of human history of pancreatic transplantation dating from December 1966 the therapy remains highly investigational. The possibility of successful islet transplantation in the cure of juvenile diabetes mellitus is, at present, the major thrust in the therapy of the disease. However, it would appear that parallel programs are needed to define the potentials of the successful metabolic correction of the diabetes by one technic or the other in the order of carefully planned investigational programs, selecting well informed subjects. The vascularized pancreatic graft has clearly been capable of rendering a diabetic normoglycemic. However, the small number of pancreas transplants done by any one group in part as a result of a lack of commitment to this technic and the difficulty in satisfactory organ procurement in other areas of the country have made it difficult to give a proper perspective of what pancreas transplantation can offer to the juvenile onset diabetic with the early progression of nephropathy, to this time. With the best worldwide information available today there are only four pancreatic allografts alive, one beyond three years and the other three less than one year. To establish any perspective on the human potential a significantly larger group of patients will have to receive transplantation before any decisions can be made with regard to the potential for aborting the serious multi-organ complications of the disease.

SENSORS AND THE ARTIFICIAL PANCREAS

A. M. Albisser, Ph.D.

Sensors have a role in present day research and a role in future implantable systems either for totally automated insulin delivery or possibly for self-treatment.

Sensors in the form of present day blood glucose analysers are more than adequate for short term studies of one to two day's duration. They can be coupled to diabetic subjects in the clinical setting and adapted to draw minute volumes of blood in which the glucose concentration can be measured by methodologies employing enzymes such as glucose oxidase or catalysts such as the noble metals. Implantable versions of such blood glucose sensors are now under development in the laboratories of Dr. S. Soeldner and Dr. S. Bessman. However, their bio-compatibility and performance when implanted in vivo either in blood or tissue remains to be assessed.

Although I have a long standing interest in blood glucose sensors my interests relate more to the total problem of the restoration of blood sugar regulation in diabetes using complex systems of instrumented devices. Ten years ago when I started to work on this approach with my colleague Dr. B. S. Leibel, the level of technology was just adequate to enable the construction of such an instrumented system, but it was not done - why? In retrospect it is clear that the thrust of research was towards physiological studies of carbohydrate homeostasis and its mathematical modelling. In the intervening interval the research community learned a great deal about the physiology of the gluco-regulatory system and developed some highly complex and exhaustive computer models, but they ignored the pathology probably because new tools for its study were not available. Recognizing this need we developed a system which includes three components serially connected in a closed loop fashion to a diabetic subject. The three components are a blood glucose sensor, a computer and a hormone delivery system. Applied first to animal subjects, it succeeded in regulating the glycemia of pancreatectomized dogs. With further studies in these subjects, the system was improved and in due course applied to humans where it has been uniformly successful in restoring ideal stability to the diabetic subject. Now an instrumented system of laboratory devices exists which can restore blood sugar regulation in diabetic patients and the doors have been opened to the further study of the pathology of the disease. To demonstrate the potential of this area of research I will present some of the results of our current clinical investigations using the new system. Laboratories and clinical investigation facilities with such capabilities have been established

in Toronto, Canada, at The Hospital for Sick Children, The Mount Sinai Hospital and the Toronto General Hospital; in Ulm, West Germany, at the University of Ulm; in Sydney, Australia, at St. Vincent's Hospital; and in Tokyo, Japan, at the University of Tokyo. To the best of my knowledge, none is in existence in the United States of America at the present time.

FUTURE NEEDS

Before any sensors are ever implanted in diabetic subjects fundamental research must be done to verify their applicability either for diabetes self-treatment or as components in automated insulin delivery systems. Rather than wait for the development of an ideal sensor or the perfect hormone delivery pump, I recommend that short term studies be undertaken to expand the clinical knowledge of the pathology of the disease. More basic information is needed regarding the details of the glycemic patterns in diabetics and how these are affected by diet, exercise and emotional stress when the patient is treated with subcutaneous insulin and when insulin is delivered intravascularly according to need by a clinical extracorporeal artificial pancreas. Therefore, I recommend that funds be provided to establish at least two and perhaps as many as five laboratories to carry out investigation into the pathophysiology of diabetes using systems of instrumented devices for blood sugar regulation, and that the thrust of these investigations be directed to bear on the potential problems of future implantable devices. Such a directed effort of fundamental research will define the functional defects in diabetes and thereby enable the precise specifications for the instrumented devices needed to rehabilitate the patient. Technology can then be called upon to produce the required components and integrate these to form an implantable artificial endocrine pancreas.

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PROGRESS REPORT ON THE ARTIFICIAL BETA CELL

Samuel P. Bessman, M.D.

It is our view that the complications of diabetes are brought on
primarily by an imbalance between the amount of insulin required from
moment to moment and the amount of insulin now given as single doses
one, two, or three times a day. Since the emission of insulin from the
pancreas is neither constant, nor is it a few single doses per day, a
regularly treated diabetic either has too much or too little insulin
available at all times. The normal effect of insulin is primarily
anabolic and acts to repair the tissue destruction caused by the
stresses of living. It is therefore our opinion that the blood sugar
concentration is a signal for the emission of insulin and the objective
in the care of the diabetic is not to normalize the blood sugar to some
constant point but to respond, with insulin, to the body's needs as
signaled by the blood or tissue sugar.

In order to maintain any similarity between the administration of
insulin therapeutically and that done by the normal pancreas we have
to know not only when insulin is necessary -- a reading of the blood
sugar -- but we must also know how much to give. We presume this
amount would vary depending upon the rate of administration and the rate
at which we wish to have the blood glucose fall. We must never give an
excess of insulin. If we give an excess of insulin then the patient
will suffer from hypoglycemia. The normal individual has the ability
to respond to slight excesses of insulin with an emission of glucose
but is not able to overcome large excesses perhaps of even a few units
per hour. For this reason a very precise feedback system is required
for any prosthesis to replace beta cell function in the diabetic.
Furthermore, in view of the fact that the major cause of fluctuations in
the diabetic is stress, any addition to the stress of the diabetic by
calling his attention to the blood sugar would seem to us to be self-
defeating. For this reason we have developed our research program to
produce a complete feedback system, not as its final goal, but as its
only goal.

Research has proceeded in our laboratory along three lines. We have
developed a sensor for blood or tissue glucose, a mini-computer to inter-
pret the signal from the sensor and to control the third part of the
system, a pump small enough and accurate enough to serve the purpose of
an implanted artificial organ. These three parts will be described
below.

THE SENSOR

This is a separate unit about the size of a five cent piece and about twice its thickness. It contains two galvanic oxygen-type electrodes with polypropylene membranes. These oxygen electrodes have been tested for long periods of time in animals and represent the most stable implantable oxygen electrodes that are now available. They maintain their stability for many weeks and have been kept, in long term tests, up to six months in the abdominal cavity of a rabbit without loss of activity. The pair of electrodes is designed to produce the same current for the same oxygen tension and they are balanced against each other. In order to make the glucose sensor we attach to one electrode, by silicon glue, a disk of plastic cloth to which is chemically bonded an enzyme, glucose oxidase, which specifically reacts to consume glucose and oxygen. The more glucose present the more oxygen the enzyme consumes.

Since only one of the oxygen electrodes is shielded by glucose oxidase, the glucose in the tissues, by causing oxygen at one electrode to be depleted, will cause the two electrodes to read differently and the difference between them is a function of the tissue sugar. This electrode has been used to measure sugar continuously in the blood of rabbits over periods up to 18 hours and many glucose tolerance curves have been performed on these animals. A paper has been submitted for publication to "Diabetes" on this subject. Over 200 glucose electrodes of this general design have been made and tested.

THE PUMP

The pump is a unique design using a bellows arrangement of two piezoelectric disk benders facing each other on a ring of plastic. When a positive voltage is applied the two benders move toward each other and with a negative voltage they expand apart, giving a bellows, or medicine dropper, action. The benders are coupled to a microvalve through a phase shifting arrangement in order to produce sequential squeezing of the bellows and shutting of the valve. The valve displaces approximately 50 microliters and the volume pumped per stroke is approximately 1/10 of a microliter. This entire unit is about as large as a half-dollar and approximately 5/8" thick.

One A battery will supply sufficient power for this pump to pump insulin at the average rate of 30 units per day for about 6 years. Four working models of this pump have been constructed and the physical characteristics and general structure are described in an article in press in the Proceedings of the American Society for Artificial Organs. A copy of this is attached.

THE COMPUTER

The computer is designed to produce a frequency signal in some non-linear relation to the glucose signal emitted by the sensor. Various configurations of this computer circuit are under test. These will resemble somewhat the program of Albisser and Pfeiffer but under no circumstances will they be designed to give insulin at a rate which will result in hypoglycemia or too rapid fall in the blood sugar. The way this is being done is to make certain aspects of the computer program adjustable so that the computer can be tailored to the individual animal or patient at the bedside.

CURRENT STATE OF DEVELOPMENT OF THE ENTIRE ARTIFICIAL BETA CELL

A working model of the artificial beta cell measuring 4" x 4" x 2" including a power supply, sensor, computer, and pump will be demonstrated. This unit has been designed to emit pulses of solution equivalent to insulin of .1 microliters per pulse. The rate of emission of pulses is directly related to the glucose concentration of a test solution in which the electrode can be dipped. The model is adjusted to respond to a range of approximately from 0 to 50 milligrams percent glucose. At 50 milligrams percent the pump will emit approximately 250 strokes per minute of solution and at 0 milligrams percent it will emit nothing. The model is so arranged that there are external controls which can select operating conditions within this range. In actual use such a unit will have its frequency maximum approximately 1/200 of the above frequency but for demonstration purposes this would not provide visible information since the pulses would come at approximately one per minute.

This is one of two working models of the apparatus that has been constructed and has performed according to expectations. Two new models are being made to contain all of the parts of this apparatus within a volume equivalent approximately of a pack of cigarettes. These will be the models that will be tested in animals within the next three months. The large model which is demonstrated is being prepared with a new program for the shorter frequencies to control the diabetic animal extracorporeally.

PROBLEMS FOR FUTURE DEVELOPMENT

The major problem to be dealt with at present is the design and construction of a tissue compatible integument for this apparatus. We have done no research in this area in anticipation of utilizing the technology developed in the cardiac pacemaker research and the experience of others with other implanted materials.

The power supply will also depend upon the technology now available for the power requirement of this apparatus will be less than that of the cardiac pacemaker. The sensors themselves produce current rather than consume it.

FINANCING

This program began about 3-1/2 years ago and has been financed entirely by the University of Southern California and private donors. It is difficult to determine the exact budget consumed because the major scientists in the project, Drs. Layne, Schultz, Thomas, and Bessman, have had their salaries paid entirely by the University of Southern California. They average approximately half their total time on this project.

All of the apparatus including sensors, pump, computer, amplifiers, and flow cells for extra-corporeal monitoring have been constructed in the private workshop of Dr. Bessman and in the laboratories of the Department of Pharmacology at the University of Southern California.

All parts used have either been constructed or bought off the shelf as items of commerce. Recording devices, pumps, and other standard items have been purchased through donations from private individuals.

A computer, PDP-11, has been purchased through a private organization and is used to monitor ongoing animal experiments and design circuitry for the micro-computer system. There are no commercial interests in this development program.

Any patents will be the property of the University of Southern California assigned by the inventors in this group.

The private funding for the first year was approximately $15,000; the second year about $20,000; the third year $160,000, and the fourth year approximately $60,000. All costs of the private machine shop are donated.

FUTURE NEEDS

The animal experimentation will become more expensive as the working models of the Artificial Pancreas are produced and tested. For the program to develop at optimum rate we would expect to test the unit in 100 dogs at least over the next year. This would require at least two people with biological and surgical training and a great deal of animal care. We estimate the costs of such an expanded item to be

approximately $60,000 per year including costs of animal care, purchase of animals and personnel. The human monitoring using the glucose electrode extra-corporeally will require one full-time medical person and the construction of several monitoring amplifiers with recorders. This should cost approximately $40,000 per year.

Permission has been granted to our group by the Human Experimentation Committee for the experiments in extra-corporeal monitoring.

Rapid experimental development of the unit will require the services of a full-time electronic technician and a machinist. These individuals with supporting costs should be approximately $50,000 per year. Materials and parts should cost approximately $20,000 per year and recording devices, pumps, and support equipment another $35,000.

It is our belief that the Department of Pharmacology could benefit in its teaching program from the presence of at least one person to take the place of the large amount of time spent by the senior personnel and this would be an item of approximately $30,000 per year.

POTENTIOMETRY, POLAROGRAPHY, AND FUEL CELLS

Leland C. Clark, Jr., Ph.D.

PART I TECHNICAL

The author's technical comments concerned very briefly explaining the principles of polarography, potentiometry and the fuel cell. The three basic concepts are very easy to understand.

1. Potentiometric, or voltage measuring
2. Polarograph, or current measuring
3. Fuel cell, a hybrid between numbers one and two

1. Potentiometry. The concept of measuring voltage differences between two electrodes as a means of detecting the concentration of a substance in a solution was born before the 1900's. It remained for Nernst in the early 1900's to elucidate the theoretical aspects of the voltage (EMF) developed with the still famous Nernst equation.

2. Polarography. Heyrovsky received the Nobel prize in chemistry in 1960 for work begun in 1922 for similarly elucidating the principles of polarography.

3. Although the first fuel cell was described in 1839 by Grove, and even Nernst in 1912 received German patents on a fuel cell, it was not until about 1932 when Bacon in England made the first practical five kilowatt hydrogen/oxygen fuel cell. Much of the research in the past several decades has concentrated on using the fuel cell as a no-moving part, highly efficient source of power. In this workshop the fuel cell principle is used to measure glucose concentration, not to report it as such, but to drive an insulin pump. The more glucose, the faster the insulin pump will run.

Of course, all three principles have in common that somehow a chemical event is directly translated into an electrical event. In biomedical research the most important electrodes are those that measure pH, pCO_2, and pO_2. But ion-specific electrodes and enzyme electrodes are rapidly gaining an important function as electrochemical sensors in health research.

Polarography, a science which began in 1922, is based upon controlling the voltage and measuring the current (a flow of electrons). Potentiometry is simply the measurement of voltage. To accurately measure the voltage (a pressure) the least current used the better

because the current saps the voltage. As examples, the Clark oxygen electrode uses the polarographic principle while a pH electrode uses the potentiometric principle.

In polarography, at a fixed voltage, the current flow is proportional to the concentration of the substance being measured, that substance either gains or loses electrons to produce the current flow. At an oxygen cathode (an electrode connected to the negative pole of a battery) electrons are donated to the oxygen and at a rate proportional to the oxygen contacting the electrode. At a peroxide anode (connected to the positive pole of a battery) the electrons are received from a substrate, or substance being measured, at a rate proportional to the amount of substance contacting the electrode.

In chemical terms, the cathode reduces substances and the anode oxidizes.

The fuel cell is just between the two, a hybrid so to speak, where the substances being measured (or utilized for energy) produce the very voltage which is needed to produce the current. Because of the current flow the voltage may drop; but this can be made small by mechanical design and other factors, so that the voltage remains fairly constant.

Polarography gives a linear meter reading in relation to the concentration of glucose. Potentiometry gives an exponential or logarithmic relation to concentration of glucose. The Nernst equation essentially says that there is a 60 millivolt change for every 10 fold increase in concentration. The first step of ten, say going from 1 to 10 MEQ gives 60 MV, the next step, from 10 to 100 MEQ gives an additional 60 MV, then 100 to 1000 gives another 60 MV. In the first stage a 10 MEQ change gives 60 MV whereas in the second stage 10 MEQ gives only about 6 MV.

All of the three electrode systems described above are essentially not very "bright," or at least they cannot discriminate very well. There are some exceptions: The Ross-Orion fluoride ion potentiometric electrode gives a voltage change only when fluoride ion concentration changes. Glucose by itself does not give a current in a polarographic electrode. Glucose does not change the voltage of a potentiometric electrode such as a pH or ion selective electrode. It does change the voltage in a fuel cell. Let's see why.

A fuel cell has some kind, or kinds, of active metal catalyst which initiates and speeds the oxidation of glucose, for example, and during this oxidation a voltage is generated.

Catalysts work very well in an environment of pure substances, in fact they work so well under these conditions that many important

industrial processes rely upon them. The cell, which produces electrical energy by directly contacting hydrogen and oxygen and used as a source of power on spacecraft, is an example of this.

A potentiometric electrode made of, let us say a catalytic platinum black material may also catalyze the decomposition of glucose to produce a voltage.

The international standard of voltage for electrochemistry is based upon a catalytic (platinum black) electrode which uses hydrogen. About 1960 Clark used a tiny platinum black electrode on the tip of a heart catheter to detect heart defects by measuring the voltage after the patient breathed hydrogen so such electrodes can work, at least for a few weeks or months, albeit with possibly decreasing response, in contact with whole blood.

Basically, though, all of the above electrodes are, as I say, not very bright. They become intelligent only when specificity is conferred. And this can be done by enzymes, as first shown by Clark and Lyons in 1962.

Coupling enzymes with electrochemical electrodes has begun a new field of analytical chemistry. The enzymes can either act in a solution of the substance being measured or can be trapped near the electrode as by using a sheet of cellophane over the enzyme which is placed on the sensing end of the electrode. Recently it has been shown that enzymes can be altered chemically so that they are more stable and long lasting. Further this chemical immobilization process can be used to actually fasten the enzyme directly to the membrane. The advent of immobilized enzymes has greatly amplified the future of analytical enzyme electrodes because the enzymes can not only now be fastened where they are needed but they can be made very stable and robust.

The history of electrodes which directly contact body liquids, such as blood or extracellular fluid, is that their sensitivity gradually decreases. The reasons for this vary with the type of electrode used. Among the reasons for this electrode fatigue are, body proteins physically plugging pores in membranes or coating electrode surfaces, trace metals in blood changing the surface nature of the electrode by plating out and sulfur compounds "poisoning" the active electrode surface.

It may be that a means can be found to periodically calibrate a subcutaneous or indwelling glucose sensor, for example by withdrawing a blood sample, analyzing it, then turning a knob via a magnet over the skin. Such knob-turning has been done with pacemakers and calibration of indwelling pO_2 electrodes has been accomplished.

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There are essentially no problems involving electronic circuits and probably none involving mini-computers.

The above technical details are necessary to understand what will happen in the future. They are necessary to understand in order to set goals for the future of research to speed the treatment of diabetes.

Summary

Doctor Clark stated that although enzyme-based electrochemical glucose sensors are already an accurate, sensitive and rapid practical reality in as clinical analytical methods they leave much to be desired in long term stability. Hence research is needed for ways to stabilize glucose sensors before an implantable artificial pancreas can be made. Much can be learned in the meantime by continuous monitor and control of blood glucose by external measuring, computing, and pumping devices.

PART II GENERAL

Doctor Bessman reported on the development of an electrode system for measurement of glucose where the signal can be programmed so as to control the injection of insulin by an ingenious ultra micro pump. His electrode, according to Doctor Clark, has the advantage that it requires no direct contact of blood or tissues with the actual electrode surfaces. In essence his electrode senses the difference in voltage between two isolated chambers one of which has glucose oxidase, an oxygen and glucose consuming enzyme wall while the other is simply plastic membrane with no enzyme. Because of this, a battery or fuel cell is produced as a result of this difference in voltage between the enzyme coated chamber and the uncoated chamber. This voltage should vary with the concentration of the glucose contacting the electrode system. It can be made about the size of a dime. Doctor Bessman reported that there were a little less than a thousand of these sensors made by him personally in a home garage type of situation.

Doctor Bessman reported that his high publicized glucose catalytic sensor has been abandoned. Doctor Bessman feels that the major obstacle to future use of his "artificial pancreas" is in finding a means to test it clinically. Doctor Clark thought that a further major obstacle might be in proving its stability and getting FDA approval.

Doctor Soeldner described his fuel cell electrode system for use as a part of an "artificial pancreas." His report consisted mainly of sketches of various combinations of a multiple sandwich type of sensor where glucose could penetrate one disc, through a cellulose acetate membrane, and oxygen on the other side through an electrolyte

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impermeable, but oxygen permeable membrane, with the combination gener-
ating a voltage. The original sensor of this type described by
Soeldner's group has apparently been abandoned since new designs and
configurations were presented. No data as to the performance of the
new sensor design were given. But old data showing that such a fuel
cell electrode would function to report blood glucose levels when
implanted subcutaneously in the rabbit were presented. Doctor Soeldner's
contribution so far is to show that a subcutaneous glucose electrode may
reveal blood glucose levels.

Doctor Bessman said that it makes a difference whether the glucose-
sensitive side of the implanted sensor faces the muscle or the skin.

Doctor Clark said there was an urgent need to find out if where a
sensor, whether it be electrochemical or otherwise should be placed.
There were some comments that it should be intravascular, and other
comments that it should be portal.

Tom Davis seemed to be worried about the volume of the package used
to contain the sensors. Perhaps also concerned about mass production
of sensors. He described in great detail a number of chemical and
mechanical steps to produce a sensor which requires no housing. The
complex sandwich leading to the final sensor has not yet been tested
once -- even in a glucose solution!

Doctor Albisser summarized his findings of studying patients by with-
drawing micro streams of blood from patients through an analytical in-
strument, a mini-computer, and an insulin (possibly also a glucagon and
glucose) pump. He introduced data to show that it is not sufficient to
have an apparatus, which will inject insulin when the blood glucose
increases but that the device must have enough intelligence to take
into account the rate at which the changes are occurring. He showed
theoretically that a relatively simple device could be made to perform
this task. The interesting studies of Doctor Albisser must give pause
to those who want to make a device which will program in insulin based
upon blood glucose on some kind of a linear, perhaps with a delay,
insulin-inject-if-blood-glucose-is-too-high-and-stop-before-it-gets-
too-low.

In general it appears that none of the three types of electrodes --
polarographic, potentiometric, or fuel cell -- had been ruled out. In
fact all show promise. Lack of information on in vivo stability was the
main concern of Doctor Clark.

Finale

In terms of the magnitude of the problem of diabetes in general, and the heart rending problem of juvenile diabetes, the funds available at the NIH are pitiful indeed, they may become a national scandal in a few years.

The NIH should have a large public relations department where the problem of diabetes is explained directly to the people. Congress has obviously been unable to deal with it effectively.

If funds were made available they could be used effectively. I know of eight bright young scientists with publications and engaging in full time research whose application for career development awards were turned down. This has a very depressing effect on these young men and women.

The American people should know that the money saved per year because there is no polio, because of Sabin, is greater than the total health research budget in the entire country. There is a long list of diseases where there has been a tremendous saving, on a similar scale.

I have just invented an electrode which will measure blood cholesterol in two minutes, for a few pennies, using only one fifth of a drop of blood. The present methods take more time and cost dollars. So even new methods can save millions of dollars a year in costs to the American public.

No research scientist, such as myself thinks that the citizens should be grateful for the past accomplishments in health and basic research and the great savings in suffering and death. But they should be made aware of the fact that it is simply good business on a national level to spend money on basic and health research. If money is not expended now for research in diabetes, billions of dollars will be wasted over the next decade. My children and grandchildren will have to pay for it.

Considerable attention should be given to creating situations and environments where scientists will be stimulated to develop new ideas and approaches to the problem of diabetes. Young people should be encouraged to do research in diabetes and basic research in cellular metabolism related to diabetes.

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A LAMINATED GLUCOSE SENSOR

Thomas A. Davis, Ph.D.

The Diabetes Trust Fund of Alabama is sponsoring a research grant in Southern Research Institute in collaboration with the Diabetes Hospital in Birmingham, Alabama, to develop a glucose sensor that will ultimately become a component of an artificial pancreas. The key component of an implantable artificial pancreas is a glucose sensor that is reliable, reproducible, compact, reasonably priced, and capable of functioning for several years while implanted in a diabetic patient. We believe that these criteria can best be met with a laminated fuel-cell-type glucose sensor. Moreover, such a sensor can be utilized for patient monitoring while researchers perfect the other essential components of the artificial pancreas (a pump, an insulin reservoir, a power supply, and the miniaturized electronic circuitry to interpret the signal from the sensor and control the rate of insulin delivery), all which appear to be attainable with current state-of-the-art technology.

A glucose sensor that employs blood glucose as fuel and blood oxygen as an oxidant appears to be a promising candidate for long-term implantation. The fuel cell can be designed so that the rate-determining process is diffusion of glucose from the blood to the anode so that the output of electrical current from the sensor is proportional to the blood glucose concentration. At the anode, glucose is oxidized to gluconic acid, electrons are released, and hydrogen ions are generated (or hydroxyl ions are consumed). On the other side of the cell, oxygen from the blood diffuses through a silicone rubber membrane to the cathode where it is reduced in the presence of water to hydroxyl ions. An anion-exchange membrane between the two electrodes allows one-way passage of hydroxyl ions to complete the internal electrolytic circuit. An external electronic circuit, connecting the two electrodes, measures the current generated in the fuel cell.

Glucose sensors of the fuel cell type that are being developed by other investigators consist of an array of membranes and electrodes clamped together. The clamping fixture will ultimately limit the degree to which the device can be miniaturized, and one-at-a-time assembly procedures will be quite expensive. In our laminated glucose sensor, the electrodes and membranes are molded together as one unit. A large number of sensors can be molded in a single sheet, thus reducing cost and increasing reproducibility. The laminated sensor is less than 1 mm thick, and its length and width can be reduced to the point of minimum acceptable current output. With sufficient reduction in width, the laminated glucose sensor may be insertable through a needle or catheter for clinical monitoring of blood glucose levels.

Our early research on the laminated glucose sensor has been directed toward developing techniques for fabricating components and molding them into one unit. A major achievement of this research has been the development of techniques for spin casting of polymeric membranes, cellulose acetate or silicone elastomer, that contain a layer of platinum black catalyst imbedded in one surface. We have also developed techniques for heat molding thermoplastic anion-exchange membranes or polymerizing anion-exchange material _in situ_ between platinum electrodes to bond the components.

The tasks that lie ahead include: selection of the best materials for membranes, catalysts, and conductors; development of membranes with the desired permeability properties; fabrication and _in vitro_ evaluation of the performance of prototype sensors; biocompatibility studies; and long-term _in vivo_ evaluation in animals. When these studies show that the sensor is safe and reliable, we plan to use it to monitor patients in three clinical settings; (a) diabetics with ketoacidosis or hyper-osmolar coma during their initial treatment period, (b) diabetic patients undergoing peritoneal dialysis or hemodialysis, and (c) patients with acute myocardial infarction while they are being treated with metabolic solutions.

We estimate that an expenditure of $300,000 over a period of three years will be required to bring the laminated glucose sensor to the point of clinical acceptability, to develop techniques for producing the quantities of sensors needed for independent evaluation by other researchers, and to wed the sensor to the other components of the artificial pancreas.

THE DIABETES CELL COLLECTION OF THE
HUMAN MUTANT CELL REPOSITORY

Ruth L. Kirschstein, M.D.

The Human Mutant Cell Repository, which the National Institute of General Medical Sciences supports under contract (N01-GM-3-2112) with the Institute for Medical Research in Camden, New Jersey, was established in 1972. Its function is to collect, maintain, and disseminate viable human cells representing a spectrum of human genetic diseases. The Repository distributes standardized, well-characterized cultures to the scientific community to facilitate research and teaching in human and clinical genetics. As it begins its fourth year of operation it is already clear that this facility is becoming an increasingly important stimulus to the advancement of clinical genetics research.

Much of the success of the program can be attributed to continuing interactions of the NIGMS Genetics Program consultants and staff with the contractor. A key element has been the in-depth input by the Mammalian Cell Lines Committee whose function is to advise the project officer in matters of policy and overall composition of the collection. This has resulted in the appointment of curators from academic institutions to oversee the assemblage of specific portions of the collection; a careful review of overall balance; a geographically separate safety backup for the holdings of the collection; the design of appropriate user guidelines and agreements to control potential biohazards; and the publication (particularly in the journal "Cytogenetics and Cell Genetics") of detailed descriptions of a number of the more unusual cultures that are available.

The Repository's most recent catalog (October 1974) lists some 331 cultures which are available for distribution. This list includes single-gene defects with emphasis on mutants of known biochemical defects, chromosome aberrations, normal control cell lines, and some animal cell lines used in gene mapping studies. Types of cell lines include fibroblasts, lymphoid cells, and several lines derived from human amniotic fluid.

The general policy of the Repository is to actively solicit and collect material of all known genetic and biochemical etiology in which the defect can be demonstrated in culture. Unlike most conditions represented by cell cultures currently maintained in the Repository, diabetes mellitus is poorly defined genetically, and a specific metabolic defect has not, as yet, been demonstrated in culture. Because of the importance of diabetes as a human disease problem, however, and the possibility that there are genetic causes of this

disorder, it was recently agreed by the Cell Lines Committee (March 5, 1975) that a collection of cell lines derived from biopsy material from carefully selected patients would be a legitimate component of the Human Mutant Cell Repository. The Director of the National Institute of General Medical Sciences has concurred with this decision, and plans are being implemented to establish the diabetes cell collection.

Undoubtedly there are a large number of different genetic mechanisms and hence sub-types of diabetes, and the problem of distinguishing between genetic and nongenetic types is difficult. It is therefore necessary to define rigid criteria for acceptance of biopsy specimens. As a general rule, skin biopsy and/or blood will be used to establish cultures from the following:

1) adults having mature onset diabetes with a familial history of the disease, and appropriate controls;

2) monozygotic twins concordant for diabetes;

3) patients with presumptive autosomal recessive syndromes known to be associated with diabetes, and who themselves have the disease; and

4) individuals whose lymphocytes have been screened for HL-A8 and W15 immune phenotypes (both of which are correlated with diabetes).

Complete documentation regarding the patient whose biopsy is received will be required, including pedigree data and, where appropriate, documented history of the age of onset, severity, and complications of diabetes.

A major premise of the project is that continued investigation of such cell lines may help to uncover biochemical bases for the etiology of genetically determined diabetes.

It is anticipated that for the foreseeable future, the Repository will be scaled up to encompass a seed collection of about 50 cell lines. The project got underway in late fiscal year 1975, with modest funding (about $5,000) from that year's budget. It is expected to operate at a level of $25,000 - 30,000 per year when it becomes fully functional in fiscal year 1976 or 1977.

It should be emphasized that this is a pilot project which will be evaluated periodically. If it is determined that such cell lines are of great use in the projected studies of diabetes, expansion will be supported.

The curator of the collection is Dr. Joseph L. Goldstein, a member of the Mammalian Cell Lines Committee, from whom further information may be obtained and who will consider recommendations for developing the collection and any ideas that are put forth.

ISLET TRANSPLANTATION*

John S. Najarian, M.D.

INTRODUCTION

Diabetes Mellitus and Endocrine Replacement Therapy: Statement of
Problem. Diabetes mellitus is one of the leading causes of death in the
United States. The majority of deaths are due to associated vascular,
renal and other complications. Exogenous insulin, as currently adminis-
tered, does not physiologically regulate plasma glucose and does not
prevent the development of these complications.

A working hypothesis providing a rationale for new approaches to the
treatment of diabetes is that these complications are truly secondary
to deranged metabolism, and that perfect regulation of plasma glucose
will prevent or halt progression of these complications. This control
could be achieved by mechanical infusion of insulin coupled to a glucose
sensing device, or by transplantation of normal islets. Our own inves-
tigations have centered around the latter approach.

It is now established that chemically induced diabetes in the rat or
mouse can be cured by intraperitoneal and intraportal transplantation
of either isolated adult islets (1-5) or of dispersed neonatal pancreas
(6,7), and that partial amelioration of diabetes can be achieved in
other species (8,9).

INVESTIGATIVE WORK OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF MINNESOTA, RELATING TO ISLET TRANSPLANTATION

Our own work includes: (1) determination of the effect that islet
transplantation has on diabetic renal disease in the rat; (2) isolation
of islets from human cadaver pancreata and investigation of infant
cadaver pancreata as a source of islet tissue; (3) quantitative studies
of dispersed neonatal pancreas transplanted to the portal vein in

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diabetic rats; (4) investigation of alternate techniques to collagenase digestion-Ficoll gradient separation for dissociation of islet tissue from pancreatic exocrine enzymes; (5) and clinical transplantation of cadaver islets in diabetic recipients already receiving immuno-suppressive therapy following kidney transplantation for end stage diabetic renal disease.

Effect of Islet Transplantation on Diabetic Renal Disease in the Rat. Diabetic renal disease in the rat is characterized by glomerular mesangial matrix thickening and hyaline nodule formation, and by mesangial deposition of macromolecules including IgG, IgM and B,C (7). Renal transplantation experiments have shown that the lesions are secondary to the diabetes and not to the inducing agent (10). Definite lesions are present by six months after induction of diabetes; ulti-mately progression to complete glomerulosclerosis occurs. Six months after induction of diabetes, nineteen rats had a simultaneous renal biopsy and curative islet transplants. Mean plasma glucose fell from 592 ± 79 mg/100 ml pre-transplant to 141 ± 22 mg/100 ml four weeks after transplantation, and thereafter remained normal. In 15 of the 19 rats biopsied between 2 to 12 weeks following transplantation there was an actual decrease in the amount of mesangial PAS positive material. In all rats IgG, IgM and B,C either disappeared completely from the mesangium or was present in trace quantities only. The increased mesangial matrix that develops in diabetic rats is similar to lesions which occur in human diabetic individuals (11). Deranged function of the mesangium exposed to the diabetic environment may be responsible for the development of glomerular pathology. Restoration of normal mesangial function, by reversing the diabetic condition, apparently halts the pathological process and allows healing of early glomerular lesions. The demonstration in the rat that diabetic renal lesions can be reversed, or their progression halted by islet transplantation, provides a rational basis for islet transplantation in man in an attempt to halt progression or prevent development of the secondary complications of diabetes.

Isolation of Human Islets from Adult Cadaver Pancreata. Over 80 adult pancreata have been processed by variants of the collogenase digestion-Ficoll gradient separation technique (8,12). The assumption has been made that tissue insulin content is proportional to the amount of islet tissue, and that tissue amylase content reflects pancreatic exocrine tissue digestive enzyme content. The adult whole pancreas contains an average of 136 ug insulin/gm of tissue with a total insulin content averaging 6500 ug; 4.2 mg amylase/gm of tissue with a total amylase content of 200 mg; and an insulin/amylase ration (I/A) of 30 ug insulin/mg amylase. The average I/A ration of tissue isolated by the collagenase digestion-Ficoll gradient separation technique was 805, indicating significant purification of islet from exocrine tissue. The total insulin content of the isolated tissue varied from > 1% to 50% of

the whole pancreas, but was > 8% on only half of the isolation procedures. Average insulin content of the isolated tissue was 5% of that present in the entire pancreas. The several variations in technique employed for isolation all resulted in an extremely wide range in yield from one occasion to another, and increasing experience with the techniques has not been associated with a significant increase in the ability to obtain a consistently high yield of islets.

Human Infant Pancreas. Analysis of 10 infant pancreata ranging in age from a 26 week old fetus to a 17 month old infant revealed that these pancreata shared the same characteristics as described by Leonard et al (13) for the neonatal rat pancreas: high tissue insulin content and low exocrine digestive enzyme content. The human infant pancreas contains an average of 905 ug insulin/gm of tissue. Total insulin content averaged 1553 ug. Average amylase content was 0.72 mg/gm of tissue, and the I/A ratio averaged 17,427, an exceedingly high ratio when compared to adult pancreas. After dispersion of the pancreas by mincing and collagenase digestion, the total tissue insulin content averaged 388 ug with an average I/A ration of 22,800. These values are higher than what can be achieved by Ficoll gradient separation of islet tissue from adult pancreas. Dispersed human infant pancreas may be as suitable for transplantation as is the neonatal rat pancreas.

Portal Vein Transplantation of Dispersed Neonatal Rat Pancreas: Quantitative Studies. Neonatal rat pancreas has an average tissue insulin concentration of 526 ug/gm of tissue (adult=162), an average insulin content of 11.5 ug (adult=102), and an I/A ratio of 288 (adult= 7). Following dispersal by the Leonard technique (6), average total insulin content of one neonatal pancreas was 3.1 ug, representing only 3% of an adult pancreas insulin content. Twenty-five rats were transplanted with various quantities of dissociated neonatal pancreatic tissue obtained from 2 to 10 donors. Kemp et al (3) had previously shown that infusion of islets into the portal vein was more efficacious than transplantation intraperitoneally, and therefore the portal vein route was used for our quantitative studies. Although the length of time for plasma glucose to return to normal following transplantation was inversely proportional to the amount of tissue transplanted, all 25 rats were cured of diabetes, including those transplanted with as few as two dispersed neonatal pancreata. The demonstration that dispersed neonatal rat pancreas (with the islet component unseparated), containing only a fraction of the tissue insulin content of an adult pancreas, can be infused into the portal vein and cure diabetes suggests that infant human pancreas might also be a superior source of islet tissue for transplantation.

Alternative Approaches for Depleting Pancreatic Tissue of Exocrine Digestive Enzymes. Infant pancreas can be dispersed and transplanted as a free graft without separating islet and exocrine components because of the low digestive enzyme content of its exocrine tissue. Adult pancreas cannot be similarly dispersed and transplanted because of the high exocrine enzyme content of older pancreata. It is possible that adult pancreas could be dispersed and transplanted as a free graft without separation of the islet and exocrine components, (thus eliminating the extensive loss of islet tissue associated with attempts to purify islets) if the exocrine tissue could be depleted of enzymatic content prior to transplantation. Preliminary results in our laboratory have shown that pretreatment of donor rats with pilocarpine (a parasympathomimetic agent) stimulates an extreme secretory response of the exocrine pancreas, acutely depleting the pancreas of exocrine enzymes and increasing the I/A ratio. Using another method, short term tissue culture of minced, adult human cadaver pancreas (10-18 hrs) with Trasylol added to the media was associated with a depletion of tissue amylase content, maintenance of tissue insulin content, and an increase in the I/A ratio. Both these approaches could lay the basis for a method to allow dispersed adult pancreas to be transplanted as a free graft.

Clinical Islet Transplantation. A small number of diabetic patients (total of seven) who had previously received a kidney transplant for end stage diabetic nephropathy and who were therefore on immunosuppressive therapy, have received an islet transplant at the University of Minnesota. The transplants have been performed under the guidelines approved by our University Committee on the Use of Human Subjects in Research. Either Ficoll gradient separated adult islets or dispersed infant pancreata were used, and in each case the total tissue insulin content of the transplanted tissue was only a few percent of that present in a normal adult pancreas. No patients have been cured by the transplant, but most have experienced a decrease in exogenous insulin requirements at some time in the post transplant period. In three patients a prolonged decrease in insulin requirement to half of the pre-transplant level occurred and in one, the decreased requirement has been sustained for several months. In no patients have any adverse effects occurred, and the transplanted kidney has maintained normal function in all patients. Although transplanted islets may have been rejected in certain instances, in no patients has a concomitant rejection of the transplanted kidney occurred. We think further trials using larger quantities of islet tissue are justified by this early experience.

An interdisciplinary research program directed toward either curing diabetes or ameliorating the morbid and lethal complications of the disease should be supported on a national level.

Two broad approaches should be pursued: one designed to elucidate the pathogenesis, environmental and genetic, of diabetes, with ultimate application in disease prevention; the other directed towards development of new treatment approaches, including implantable insulin pumps coupled to a glucose sensor and pancreatic or islet transplantation. Research efforts in several institutions, pursuing these goals from many approaches, should be most fruitful.

Centers to receive major funding should have a large clinical population of diabetic patients. It is the problems these patients present that provide the stimulus for research. In each of those centers several professional individuals representing various departments should be actively involved in a diabetes research program.

Money should be allocated to cover both basic animal research and to cover patient care costs in centers where human subjects will be included in research programs, as approved by the centers' committee on Use of Human Subjects in Research. We feel it is very important to include funds for clinical trials of new treatments in centers with the appropriate capability and associated research program.

When large scale trials of newer treatments are possible, increased funding will be essential, especially to support controlled studies allowing analysis of the vascular and other associated complications of diabetes in patients treated by new techniques as compared to those receiving standard treatment.

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THE GLUCOSE MONITOR -- ARTIFICIAL BETA CELL PROGRAM

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INTRODUCTION

There is a great deal of concern currently focused upon the chronic complications of diabetes mellitus. Associated with this is a controversy regarding the underlying etiology of these complications. There appears to be an increasing mass of evidence that suggests that the fundamental basis of these complications may be related to the fact that in the greater bulk of diabetic patients, blood sugar and/or insulin levels are not in the normal range and/or appropriately related to each other on a moment to moment basis throughout the day. This has stimulated many laboratories, including our own, to think in terms of a novel therapeutic approach that might restore in the diabetic patient normal and appropriate levels of glucose and insulin throughout the day. Some laboratories have focused upon the development of a tissue transplant or implantation program supplying to the diabetic a normal mass of beta cells. Other laboratories have focused upon an artificial miniature implantable device or larger non-implantable, external support systems for controlling and normalizing blood sugar levels. In addition, efforts in one laboratory have been focused upon a blend of tissue and device technology.

The particular path chosen by this project has been exclusively focused upon a miniature implantable device. The first phase of this project has been the development of a miniature totally-tissue-implantable glucose sensor. The second phase has been the development of a miniature power supply-radio telemetry system to which this glucose sensor could be attached and the entire unit ("Glucose Monitor") implanted subcutaneously and which would automatically and continuously communicate to a small portable receiver for the translation of the transmitted information to a glucose concentration value. The third phase of the program will be the design, fabrication and testing of a totally-implantable insulin delivery system consisting of a glucose sensor, a miniature computer interface for the interpretation of the glucose levels and rates of change as sensed by this miniature sensor, and an insulin reservoir and pump-delivery system.

Following a series of appropriate feasibility studies, it was felt that efforts should be focused on a miniature, catalytic-type electrode. Using the principle of platinum-catalyzed oxidation of glucose, and measuring the value of the limiting current produced by such a catalytic anode, feasibility studies demonstrated that the value of the limiting current under certain specific conditions correlated with the glucose concentration. Also, an oxygen-type cathode of certain specific dimensions was identified with an appropriate ion-exchange membrane layer separating the anode and the cathode compartments. An additional requirement was the identification of specific semi-permeable membranes to cover both the glucose anode and the oxygen cathode of the device to achieve proper diffusion kinetics and bio-compatibility. Finally, it was recognized that a third pulsing electrode would be required to prevent degradation of the platinum glucose anode.

After suitable short-term in-vitro studies were performed demonstrating the functionality of the glucose sensor, a series of feasibility studies implanting 1 to 8 glucose sensors subcutaneously in animals was undertaken. The sensor was attached via wires to appropriate amplifier-recording systems, the animals (approximately 80 Rhesus monkeys, 15 dogs, and 20 rabbits) were suitably maintained and restrained, and periodically, following the administration of glucose by vein or by mouth, the sensor current output was evaluated in juxtaposition to simultaneously obtained blood glucose levels.

The most successful of these studies in a Rhesus monkey proceeded over 117 days prior to failure of the wires connecting the sensor to the external recording apparatuses. Evaluation of these early studies indicated that the potential of this glucose sensor for long-term measurement of glucose levels in the extracellular fluid compartment could not be fully determined due to the extremely high failure rate of the connecting wires, the common occurrence of animal pull-out of these wires, and the equally common occurrence of infection initiating at the points in which the wire penetrated the skin of the animal.

It was felt that the wire-system had to be eliminated and a totally-implantable testing system therefore evolved which basically was the design and testing of a miniature power-supply radio-telemetry system with an appropriate external receiver.

Long-term (1 year) studies of the glucose sensor with the power-supply radio-telemetry system (Glucose Monitor) are being planned. Prior to the initiation of this study, certain final improvements of

the components of the glucose sensor will be made. These include the incorporation of a newly-identified glucose diffusion membrane for the glucose fuel anode (polyurethane) and the utilization of a scintered-platinum material for the glucose anode. In addition, this new generation glucose sensor will be evaluated in-vitro prior to the animal implantation studies by a special testing system which has the capability of maintaining chronic sterility and simulating physiologic and unphysiologic changes of glucose for a 90-day period.

IN-VIVO ANIMAL TRIALS

It is planned to evaluate in 40 Rhesus monkeys an equal number of Glucose Monitors for a period of one year. In summary, each animal's Glucose Monitor will communicate every 15 minutes with an external receiver unit which then relays this information to a basic computer recording system. Approximately every 2 weeks, in rotation, each animal is removed from a free-ranging cage and put into restraint for an extensive 48-hour period during which blood glucose measurements are made synchronous with each signal transmitted from the Glucose Monitor. During this period of time, glucose will be administered by mouth or by vein so that appropriate perturbations of blood glucose levels are achieved.

A tentative budget for the long-term animal studies is appended. One item, however, is still under consideration, and that is focused upon the appropriate collection of biological data that will document the long-term safety and lack of toxicity of the device in the animals which will be required before commencing clinical trials.

CLINICAL HUMAN TRIALS

After appropriate evaluation and approval, clinical trials will commence. Attached is a tentative budget itemizing identifiable costs based upon 30 patients over a one-year period. Similar to the animal trials, finalization of the costs for the collection of biological data focused upon safety and lack of toxicity has not yet been determined.

This same basic format employed for the animal studies will be utilized in the clinical trials of the glucose monitor. Between in-patient and/or out-patient evaluations of the relationship of blood

glucose to the glucose monitor signal, each patient will be provided with a portable chronic data-collection system.

THE ARTIFICIAL BETA CELL
(Insulin Delivery System)

A great deal of time has been spent by this group in discussing and dialoguing and attempting to identify already fabricated and/or tested reservoir-pump drug-delivery systems. An active interchange of information and multiple meetings have been held between various members of the Joslin-Space Sciences group and individuals involved in the development of an implantable drug-delivery system (Dr. Henry Buchwald, Department of Surgery, University of Minnesota; Dr. Perry J. Blackshear, key individuals of the Metal Bellows Co., Sharon, Massachusetts). With the information at hand, it appears quite feasible that a closer interdigitation of the work of this group into the work of the previously identified reservoir pump-system group could be implemented.

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